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(54) Title: COMPOUNDS HAVING AFFINITY FOR THE VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR-2 (VEGFR-2) AND ASSOCIATED USES

(57) Abstract: Novel compounds are provided that bind to VEGFR-2. The novel compounds have a peptide chain approximately 8 to 40 amino acids in length that binds to VEGFR-2, or are dimers of such peptide chains. The compounds are useful as probes for affinity screening and as angiogenesis imaging agents. In addition, those compounds that are antagonists of VEGFR-2 are useful in the treatment of diseases including cancer, retinopathy, rheumatoid arthritis and others. Pharmaceutical compositions and methods of use are provided as well.

COMPOUNDS HAVING AFFINITY FOR THE VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR-2 (VEGFR-2) AND ASSOCIATED USES

TECHNICAL FIELD

The present invention relates generally to novel compounds that have affinity for the vascular endothelial cell growth factor receptor-2 (VEGFR-2). More particularly, the invention relates to such compounds which act as modulators of vascular endothelial cell growth factor (VEGF) function. The invention additionally relates to methods of using the novel compounds and pharmaceutical compositions containing a compound of the invention as the active agent. The invention has application in the fields of biochemistry and medicinal chemistry and particularly provides inhibitors of VEGF function for use in the treatment of human disease.

BACKGROUND ART

Blood vessels serve an important role in the circulatory system of humans and many animals. In mammals, the internal surface of a blood vessel is comprised of endothelial cells. These cells are well-suited for imparting a smooth and "non-adhesive" or "non-tacky" quality to the internal surfaces of blood vessels. This smooth and "non-adhesive" internal surface is critical for the free flow and transport of blood and related materials through the entire circulatory system. Without such a smooth internal surface, blood vessels would become obstructed as thrombi or other blockages form at "sticky" locations on the internal walls. Such obstructions can result in partial or even complete blockage of the blood flow necessary to maintain normal tissue and organ functioning. Thus, endothelial cells serve not only an important structural component of blood vessels, but also provide blood vessels with a smooth and non-tacky internal surface.

Blood vessel formation takes place in response to stimuli in the form of specialized growth factors. These growth factors induce mitosis in cells already present in blood vessels. The newly formed cells replace damaged cells or extend the length of the blood vessel. This process of growing blood vessels from preexisting endothelial cells is termed "angiogenesis."

As its name suggests, vascular endothelial cell growth factor (VEGF) is involved in endothelial cell proliferation. VEGF is also referred to as "vascular permeability factor" or "vasculotropin." VEGF is a glycosylated dimer having an overall apparent molecular mass of about 46 kDa (the apparent molecular mass of each subunit is equal to 23 kDa). This important protein selectively induces mitosis of vascular endothelial cells resulting in endothelial cell proliferation and consequently, angiogenesis. Since blood vessels comprise, in part, endothelial cells, VEGF is required for the formation and maintenance of blood vessels.

VEGF acts on the extracellular portion of VEGFR-2 expressed on vascular endothelial cells. Thus, once VEGF binds to VEGFR-2, a signal is sent to the nucleus of the endothelial cell instructing it to divide.

As indicated above, vascular endothelial cell proliferation is desirable and necessary in a number of contexts. In other situations, however, angiogenesis is deleterious to an organism's overall health. For example, continuous angiogenesis can cause or exacerbate diseases such as psoriasis, rheumatoid arthritis and retinopathy. In addition, angiogenesis makes possible continued tumor growth by vascularizing the tumor, thereby supplying the tumor, with blood and nutrients necessary to sustain the tumor's growth. Clearly then, for these and many other disorders, preventing or at least reducing angiogenesis is desirable.

One attempt at limiting angiogenesis is described in U.S. Patent No. 5,952,199. This reference describes antagonizing the action of VEGF by administering VEGF-binding receptors, thereby decreasing the amount of unbound VEGF available to bind to the naturally occurring receptors expressed on endothelial cells. U.S. Patent No. 6,011,003 describes a similar process but employs only a fragment of a VEGF-binding receptor that retains the ability to bind VEGF.

There remains a need, however, for highly active compounds that bind very specifically to VEGFR-2, both for studies of the important biological activities mediated by the receptor and for treatment of diseases, disorders and conditions that would benefit from antagonizing the VEGFR-2. The present invention provides such compounds, and also provides pharmaceutical compositions and methods for using the compounds as therapeutic agents.

DISCLOSURE OF THE INVENTION

In one embodiment, the invention provides compounds comprising a peptide chain that binds to VEGFR-2. In one aspect, the peptide chain is approximately 15 to 40 amino acids in length and contains a sequence of amino acids of formula (I)

(I) $X_1CX_2X_3X_4X_5X_6GX_7X_8X_9CX_{10}X_{11}X_{12}$ (SEQ ID NO: 1)

wherein each amino acid is indicated by standard one-letter abbreviation, and wherein X_1 is S, T, Y, A, Q, V or E; X_2 is W, R, Y, G, Q or F; X_3 is P, L, T, S, A or E; X_4 is G, S, A or N; X_5 is E, D or A; X_6 is Y, F, N or A; X_7 is G or V; X_8 is V, E, F, L or M; X_9 is E, D or V; X_{10} is W, Y or F; X_{11} is S, A, E, G, T, W, V, N, K or F; and X_{12} is L, H, R, P, Q, V, M, S or I.

In another aspect, the peptide chain is approximately 8 to 40 amino acids in length and contains a sequence of amino acids of formula (II)

(II) $CX'_1GX'_2X'_3X'_4CW$ (SEQ ID NO: 2)

wherein each amino acid is indicated by standard one-letter abbreviation, and wherein X'_1 is W or G; X'_2 is P or A; X'_3 is E or D; and X'_4 is G or R.

In a third aspect, the peptide chain is approximately 8 to 40 amino acids in length and contains a sequence of amino acids of formula (III)

(III) $GWX''_1GX''_2GX''_3H$ (SEQ ID NO: 3)

wherein each amino acid is indicated by standard one-letter abbreviation, and wherein X''_1 is L, I or R; X''_2 is V, L or I; and X''_3 is E or V.

In some contexts, it is preferred that the compound comprises a single peptide chain. In other contexts, it is preferred that the compound is in the form of a dimer, i.e. a compound comprised of two peptide chains that may or may not be identical.

It is preferred that the compounds of the invention include a peptide having its N-terminus coupled to a polyethylene glycol molecule. Peptides having an acetylated N-terminus and/or an amidated C-terminus are also preferred.

In a further embodiment of the invention, a pharmaceutical composition is provided that comprises a therapeutically effective amount of a compound of the invention in combination with a pharmaceutically acceptable carrier.

In an additional embodiment, a method is provided for treating a patient who would benefit from administration of a VEGFR-2 antagonist, the method comprising

administering to the patient a therapeutically effective amount of an antagonist compound of the present invention.

In another embodiment, a method is provided for imaging and assessing neovascularization during angiogenesis comprising the steps of administering to a patient compound of the invention to a patient wherein the compound is coupled to a detectable label to form a labeled compound, allowing the labeled compound to bind to VEGFR-2, and detecting the detectable label.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1-1, 1-2, 1-3 and 1-4 provide the sequences of representative peptide chains contained within the compounds of the invention.

MODES FOR CARRYING OUT THE INVENTION

I. DEFINITIONS

It is to be understood that unless otherwise indicated, this invention is not limited to specific peptide sequences, molecular structures, pharmaceutical compositions, or the like, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a novel compound" in a pharmaceutical composition means that more than one of the novel compounds can be present in the composition, reference to "a pharmaceutically acceptable carrier" includes combinations of such carriers, and the like.

In this specification and in the claims that follow, reference will be made to a number of terms which shall be defined to have the following meanings:

Amino acid residues in peptides are abbreviated as follows: Phenylalanine is Phe or F; Leucine is Leu or L; Isoleucine is Ile or I; Methionine is Met or M; Valine is Val or V; Serine is Ser or S; Proline is Pro or P; Threonine is Thr or T; Alanine is Ala or

A; Tyrosine is Tyr or Y; Histidine is His or H; Glutamine is Gln or Q; Asparagine is Asn or N; Lysine is Lys or K; Aspartic Acid is Asp or D; Glutamic Acid is Glu or E; Cysteine is Cys or C; Tryptophan is Trp or W; Arginine is Arg or R; and Glycine is Gly or G. In addition, "1-Nal" is used to refer to 1-naphthylalanine, the "2-Nal" is used to refer to 2-naphthylalanine.

Stereoisomers (e.g., D-amino acids) of the twenty conventional amino acids, unnatural amino acids such as α,α-disubstituted amino acids, N-alkyl amino acids, lactic acid, and other unconventional amino acids may also be suitable components for compounds of the present invention. Examples of unconventional amino acids include: β-alanine, 1-naphthylalanine, 2-naphthylalanine, 3-pyridylalanine, 4-hydroxyproline, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, nor-leucine, and other similar amino acids and imino acids (e.g., 4-hydroxyproline).

"Peptide" or "polypeptide" refers to a polymer in which the monomers are alpha amino acids joined together through amide bonds. Peptides are two or often more amino acid monomers long. One or more of the peptide chains disclosed herein may appear in the compounds of the present. It is also contemplated that the peptide chains disclosed herein represent only a portion of the overall peptide included in the compound.

The term "dimer" as in a peptide "dimer" refers to a compound in which two peptide chains are linked; generally, although not necessarily, the two peptide chains will be identical and are linked through a linking moiety covalently bound to the carboxyl terminus of each chain.

The term "agonist" is used herein to refer to a ligand that binds to a receptor and activates the receptor.

The term "antagonist" is used herein to refer to a ligand that binds to a receptor without activating the receptor. Antagonists are either competitive antagonists or noncompetitive antagonists. A "competitive antagonist" blocks the receptor site that is specific for the agonist. A "noncompetitive antagonist" inactivates the functioning of the receptor by interacting with a site other than the agonist binding site.

The term "modulator" refers to a compound that is either an agonist or an antagonist of VEGFR-2.

"Pharmaceutically or therapeutically effective dose or amount" refers to a dose sufficient to induce a desired biological result. That result can be alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. Preferably, the dose or amount is sufficient to inhibit or reduce the effects of VEGF and, thus, alleviate the symptoms associated with an undesired proliferation of endothelial cells *in vivo*.

The term "treat" as in "treat a disease" is intended to include any means of treating a disease in a mammal, including (1) preventing the disease, i.e., avoiding any clinical symptoms of the disease, (2) inhibiting the disease, that is, arresting the development or progression of clinical symptoms, and/or (3) relieving the disease, i.e., causing regression of clinical symptoms.

"Optional" or "optionally" means that the subsequently described circumstance may or may not occur, so that the description includes instances where the circumstance occurs and instances where it does not.

By "pharmaceutically acceptable carrier" is meant a material which is not biologically or otherwise undesirable, i.e., the material may be administered to an individual along with the selected active agent without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained.

II. The VEGF Modulators

A. Compounds of Formula (I):

In a first embodiment, the invention provides compounds comprising a peptide chain that binds to VEGFR-2. In one aspect, a compound is provided comprising a peptide chain approximately 15 to 40 amino acids in length that binds to VEGFR-2 and contains a sequence of amino acids of formula (I)

(I) $X_1CX_2X_3X_4X_5X_6GX_7X_8X_9CX_{10}X_{11}X_{12}$ (SEQ ID NO: 1)

wherein each amino acid is indicated by standard one-letter abbreviation, and wherein X_1 is S, T, Y, A, Q, V or E; X_2 is W, R, Y, G, Q, F or A; X_3 is P, L, T, S, A or E; X_4 is G, S, A or N; X_5 is E, D or A; X_6 is Y, F, N or A; X_7 is G or V; X_8 is V, E, F, L or M; X_9 is E, D, V

or A; X_{10} is W, Y, F or A; X_{11} is S, A, E, G, T, W, V, N, K or F; and X_{12} is L, H, R, P, Q, V, M, S or I.

Preferably, X_1 is S; X_2 is W; X_4 is G; X_5 is E; X_6 is Y; X_7 is G; X_8 is V; X_9 is E X_{10} is W; and X_{11} is S.

Examples of particularly preferred sequences satisfying formula (I) include, but are not limited to, the following:

SCWPGEYGGVECWSL (SEQ ID NO: 4);
SCWLGEYGGEECWSH (SEQ ID NO: 5);
TCWSGEYGGVECWAR (SEQ ID NO: 6);
SCWPGDFGGVECWSL (SEQ ID NO: 7);
YCWPGEYGGVDCWSP (SEQ ID NO: 8);
SCWAGEYGGVECWSQ (SEQ ID NO: 9);
ACWTGEYGGEECWEL (SEQ ID NO: 10);
TCWPGEYGGVECWAV (SEQ ID NO: 11);
TCWPGEYGGVECWGR (SEQ ID NO: 12);
SCWPGEYGGVECWTV (SEQ ID NO: 13);
TCWPGEYGGVECWSL (SEQ ID NO: 14);
SCWEGDNGGVECWWL (SEQ ID NO: 15);
ACWPSEYGGVECWSL (SEQ ID NO: 16);
SCWPGEFGGVECWSV (SEQ ID NO: 17);
QCWPGDYGGVDCWSV (SEQ ID NO: 18);
TCWPGEYGGEECWSL (SEQ ID NO: 19);
SCWPGEFGGFDCWSM (SEQ ID NO: 20);
VCRPGEYGGEECWSL (SEQ ID NO: 21);
SCWPAEYGGVECWSM (SEQ ID NO: 22);
SCWPGEYGGEECYWL (SEQ ID NO: 23);
ECYTNAAGVLECWVS (SEQ ID NO: 24);
TCWPGEYGGEECWSI (SEQ ID NO: 25);
TCWPGEYGGVECYSV (SEQ ID NO: 26);
SCWPGEYGGEECWSL (SEQ ID NO: 27);
SCWPGEYGGVECYNV (SEQ ID NO: 28);

SCWPGEYGGVECWKL (SEQ ID NO: 29);
SCWPSEYGGEDCFNL (SEQ ID NO: 30);
TCWPGEYGGEVCWAL (SEQ ID NO: 31);
SCWPGEYGGVDCWSV (SEQ ID NO: 32);
SCWPGEYGGVECWTL (SEQ ID NO: 33);
YCWPAEYGGVECFSP (SEQ ID NO: 34);
ACGPGEYGGEECWFV (SEQ ID NO: 35);
SCWTGEYGGVECWTL (SEQ ID NO: 36);
SCWPGEYGGEVCWSL (SEQ ID NO: 37);
VCWPGEYGGVECWNV (SEQ ID NO: 38);
SCQPGEYGGMVCWSL (SEQ ID NO: 39);
VCWPGEYGGEDCWSL (SEQ ID NO: 40);
SCFPSEYGGEDCWSL (SEQ ID NO: 41);
SCWEGEYGGVECWSI (SEQ ID NO: 42);
TC(1-Nal)PGEYGGVECYSV (SEQ ID NO: 43);
TC(2-Nal)PGEYGGVECYSV (SEQ ID NO: 44);
TCFPGEYGGVECYSV (SEQ ID NO: 45);
ACWPGEYGGVECYSV (SEQ ID NO: 46);
TCAPGEYGGVECYSV (SEQ ID NO: 47);
TCWPGAYGGVECYSV (SEQ ID NO: 48);
TCWPGEAGGVECYSV (SEQ ID NO: 49);
TCWPGEYGGVACYSV (SEQ ID NO: 50);
TCWPGEYGGVECASV (SEQ ID NO: 51); and
TCWPGEYGGVECYAV (SEQ ID NO: 52).

Other preferred Formula (I) sequences include, but are not limited to, the following:

SREVSCWPGEYGGVECWSLKE (SEQ ID NO: 53);
ARVVSCWPGEYGGVECWSLNS (SEQ ID NO: 54);
PGVVSCWLGEYGGEECWSHNY (SEQ ID NO: 55);
FPLVSCWPGEYGGVECWSLKT (SEQ ID NO: 56);
TGVVTCWSGEYGGVECWARNT (SEQ ID NO: 57);

HRVDSCWPGDFGGVECWSLSE (SEQ ID NO: 58);
VRVEYCWPGEYGGVDCWSPKP (SEQ ID NO: 59);
HQVVSCWAGEYGGVECWSQNA (SEQ ID NO: 60);
NRVEACWTGEYGGEECWELNL (SEQ ID NO: 61);
AGQVTCWPGEYGGVECWAVKY (SEQ ID NO: 62);
VTCWPGEYGGVECWGRKG (SEQ ID NO: 63);
ERVISCWPGEYGGVECWTVNL (SEQ ID NO: 64);
SRVVTCWPGEYGGVECWSLEL (SEQ ID NO: 65);
NRVESCWEGDNGGVECWWLKY (SEQ ID NO: 66);
SGDVACWPSEYGGVECWSLHY (SEQ ID NO: 67);
HWEGSCWPGEFGGVECWSVNY (SEQ ID NO: 68);
DRMQQCWPGDYGGVDCWSVDL (SEQ ID NO: 69);
HRVVTCWPGEYGGEECWSLGE (SEQ ID NO: 70);
LDVVSCWPGEFGGFDCWSMKY (SEQ ID NO: 71);
NRVLVCRPGEYGGEECWSLDY (SEQ ID NO: 72);
GGVVSCWPAEYGGVECWSMDY (SEQ ID NO: 73);
GRVESCWPGEYGGEECYWLDS (SEQ ID NO: 74);
REECYTNAAGVLECWVS (SEQ ID NO: 75);
PRVVTCWPGEYGGEECWSIKY (SEQ ID NO: 76);
ERVTTCWPGEYGGVECYSVKY (SEQ ID NO: 77);
EWVVSCWPGEYGGEECWSLKY (SEQ ID NO: 78);
KRVVSCWPGEYGGVECYNVKY (SEQ ID NO: 79);
TQVESCWPGEYGGVECWKLRY (SEQ ID NO: 80);
DGVVSCWPSEYGGEDCFNLHY (SEQ ID NO: 81);
RPSETCWPGEYGGEVCWALKY (SEQ ID NO: 82);
SYVESCWPGEYGGVDCWSVKY (SEQ ID NO: 83);
PRVVSCWPGEYGGVDCWSVKY (SEQ ID NO: 84);
KRAVSCWPGEYGGVECWTLEY (SEQ ID NO: 85);
MRVEYCWPAEYGGVECFSPRD (SEQ ID NO: 86);
SRVLACGPGEYGGEECWFVQY (SEQ ID NO: 87);
ETVESCWTGEYGGVECWTLNY (SEQ ID NO: 88);

VLEVSCWPGEYGGEVCWSLKM (SEQ ID NO: 89);
SRVEVCWPGEYGGVECWNVES (SEQ ID NO: 90);
GPVVSCQPGEYGGMVCWSLNY (SEQ ID NO: 91);
ESDVVCWPGEYGGEDCWSLNY (SEQ ID NO: 92);
GRVVSCFPSEYGGEDCWSLNY (SEQ ID NO: 93);
YQVESCWEGEYGGVECWSIKL (SEQ ID NO: 94);
RVTTCWPGEYGGVECYSVKY (SEQ ID NO: 95);
VTTCWPGEYGGVECYSVKY (SEQ ID NO: 96);
TTCWPGEYGGVECYSVKY (SEQ ID NO: 97);
TCWPGEYGGVECYSVKY (SEQ ID NO: 98);
RVTTCWPGEYGGVECYSVK (SEQ ID NO: 99);
RVTTCWPGEYGGVECYSV (SEQ ID NO: 100);
ERVTTCWPGEYGGVECYSVK(alloc)Y (SEQ ID NO: 101);
RVTTCWPGEYGGVECYSVK(alloc)Y (SEQ ID NO: 102);
ERVTTCWPGEYGGVECYSVRY (SEQ ID NO: 103);
RVTTCWPGEYGGVECYSVRY (SEQ ID NO: 104);
ERVTTCWPGEYGGVECYSVAY (SEQ ID NO: 105);
RVTTCWPGEYGGVECYSVAY (SEQ ID NO: 106);
RVTTC(1-Nal)PGEYGGVECYSVKY (SEQ ID NO: 107);
RVTTC(2-Nal)PGEYGGVECYSVKY (SEQ ID NO: 108);
RVTTCFPGEYGGVECYSVAY (SEQ ID NO: 109);
HVTTCWPGEYGGVECYSVRY (SEQ ID NO: 110);
GVTTCWPGEYGGVECYSVRY (SEQ ID NO: 111);
(Pyr)VTTCWPGEYGGVECYSVRY (SEQ ID NO: 112);
RVTTC(1-Nal)PGEYGGVECYSVAY (SEQ ID NO: 113);
ERVTTC(1-Nal)PGEYGGVECYSVAY (SEQ ID NO: 114);
RVATCWPGEYGGVECYSVAY (SEQ ID NO: 115);
RVTACWPGEYGGVECYSVAY (SEQ ID NO: 116);
RVTTCAPGEYGGVECYSVAY (SEQ ID NO: 117);
RVTTCWPGAYGGVECYSVAY (SEQ ID NO: 118);
RVTTCWPGEAGGVECYSVAY (SEQ ID NO: 119);

RVTTCWPGEYGGVACYSVAY (SEQ ID NO: 120);

RVTTCWPGEYGGVECASVAY (SEQ ID NO: 121);

RVTTCWPGEYGGVECYAVAY (SEQ ID NO: 122); and

RVTTCWPGEYGGVECYSVRA (SEQ ID NO: 123).

B. COMPOUNDS OF FORMULA (II):

In another aspect of the invention there are provided compounds comprising a peptide chain approximately 8 to 40 amino acids in length that binds to VEGFR-2 and contains a sequence of amino acids of formula (II)

(II) $CX'_1GX'_2X'_3X'_4CW$ (SEQ ID NO: 2)

wherein each amino acid is indicated by standard one-letter abbreviation, and wherein X'_1 is W or G; X'_2 is P or A; X'_3 is E or D; X'_4 is G or R.

Preferably X'_1 is W; X'_2 is P; X'_3 is E; and X'_4 is G.

Examples of particularly preferred sequences satisfying Formula (II) include, but are not limited to, the following:

CWGPEGCW (SEQ ID NO: 124);

CWGPDGCW (SEQ ID NO: 125);

CGGPEGCW (SEQ ID NO: 126); and

CGGAERCW (SEQ ID NO: 127).

Other preferred Formula (II) sequences include, but are not limited to, the following:

SDSVDECWGPEGCWLE (SEQ ID NO: 128);

YNTVENCWGPDGCWLD (SEQ ID NO: 129);

MSLVDKCWGPEGCWLE (SEQ ID NO: 130);

TITVGSCWGPEGCWLDSRY (SEQ ID NO: 131);

IFLGENCWGPDGCWLE (SEQ ID NO: 132);

IREGDMCWGPEGCWVD (SEQ ID NO: 133);

LTLVDNCWGPDGCWLE (SEQ ID NO: 134);

ESRVDDCWGPDGCWLDPIT (SEQ ID NO: 135);

VEYVANCGGAERCWLGTNM (SEQ ID NO: 136);

QDCWGPEGCWLQEQG (SEQ ID NO: 137);

VLDADNCWGPEGCWLE (SEQ ID NO: 138);
MSEVEDCWGPEGCWLE (SEQ ID NO: 139);
NCWGPEGCWLE (SEQ ID NO: 140);
SHRVDDCWGPDGCWLE (SEQ ID NO: 141);
IIEVGNCWGPEGCWLE (SEQ ID NO: 142); and
VDNCWGPEGCWLE (SEQ ID NO: 143).

C. COMPOUNDS OF FORMULA (III):

In a third aspect, the invention provides compounds comprising a peptide chain approximately 8 to 40 amino acids in length that binds to VEGFR-2 and contains a sequence of amino acids of formula (III)

(III) $GWX''_1GX''_2GX''_3H$ (SEQ ID NO: 3)

wherein each amino acid is indicated by standard one-letter abbreviation, and wherein X''_1 is L, I or R; X''_2 is V, L or I; and X''_3 is E or V.

Preferably X''_1 is L; X''_2 is V; and X''_3 is V.

Examples of particularly preferred sequences satisfying Formula (III) include, but are not limited to, the following:

GWLGVGVH (SEQ ID NO: 144);
GWLGAGEHN (SEQ ID NO: 145);
GWLGVGEH (SEQ ID NO: 146);
GWLGLGEH (SEQ ID NO: 147);
GWIGLGVH (SEQ ID NO: 148); and
GWRGIGEH (SEQ ID NO: 149).

Other preferred Formula (III) sequences include, but are not limited to, the following:

NASRISSGWLGVGVHNLSA (SEQ ID NO: 150);
SRRRHSTGWLGAGEHNLYS (SEQ ID NO: 151);
VIGRTWSGWLGVGVHNLSN (SEQ ID NO: 152);
QCGRVSSGWLGVGVHNLPF (SEQ ID NO: 153);
TNQRRSSGWLGVGVHTLSP (SEQ ID NO: 154);
GHKRASSGWLGVGVHKLSH (SEQ ID NO: 155);

HRRRMSSGWLGVGEHKLP (SEQ ID NO: 156);
SSGWLGVGVHYLSD (SEQ ID NO: 157);
QRRRSSSGWLGLGEHRL (SEQ ID NO: 158);
PQRRSSSGWIGLGVHDLFN (SEQ ID NO: 159);
SSRRASSGWRGIGEHNLYN (SEQ ID NO: 160); and
RCSSGWLGVGVHNLS (SEQ ID NO: 161).

D. SYNTHESIS OF THE PEPTIDES:

Standard solid phase peptide synthesis techniques are preferred for synthesis of the peptides of the present invention. Such techniques are described, for example, by Merrifield (1963) *J. Am. Chem. Soc.* 85:2149. As is well known in the art, solid phase synthesis using the Merrifield method involves successive coupling of α-amino protected amino acids to a growing support-bound peptide chain. After the initial coupling of a protected amino acid to a resin support (e.g., a polystyrene resin, a chloromethylated resin, a hydroxymethyl resin, a benzhydrylamine resin, or the like, depending on the chemistry used), the α-amino protecting group is removed by a choice of reagents, depending on the specific protecting group. Suitable α-amino protecting groups are those known to be useful in the art of stepwise synthesis of peptides. Included are acyl type protecting groups (e.g., formyl, trifluoroacetyl, acetyl), aromatic urethane type protecting groups (e.g., benzyloxycarbonyl (Cbz) and substituted Cbz), aliphatic urethane protecting groups (e.g., t-butyloxycarbonyl (Boc), isopropyloxycarbonyl, cyclohexyloxycarbonyl), alkyl type protecting groups (e.g., benzyl, triphenylmethyl), fluorenylmethyl oxycarbonyl (Fmoc), Alloc and Dde. The side chain protecting groups (typically ethers, esters, trityl, and the like) remain intact during coupling; however, the side chain protecting group must be removable upon completion of the synthesis of the final peptide. Preferred side chain protecting groups, as will appreciated by those skilled in the art, will depend on the particular amino acid that is being protected as well as the overall chemistry used. After removal of the α-amino protecting group, the remaining protected amino acids are coupled stepwise in the desired order. Each protected amino acid is generally reacted in about a 3-fold excess using an appropriate carboxyl group activator such as 2-(1H-benzotriazol-1-yl)-1,1,3,3 tetramethyluronium hexafluorophosphate (HBTU) or

dicyclohexylcarbodiimide (DCC) in solution, for example, in methylene chloride (CH_2Cl_2), N-methyl pyrrolidone, dimethyl formamide (DMF), or mixtures thereof.

Once the synthesis is complete, the compound is cleaved from the solid support by treatment with a reagent such as trifluoroacetic acid, preferably in combination with a scavenger such as ethanedithiol, β-mercaptoethanol or thioanisole. The cleavage reagent not only cleaves the peptide from the resin, but also cleaves all remaining side chain protecting groups.

These procedures can also be used to synthesize peptides containing amino acids other than the 20 naturally occurring, genetically encoded amino acids. For instance, naphthylalanine can be substituted for tryptophan, with 1-naphthylalanine (1-Nal) or 2-naphthylalanine (2-Nal). Other synthetic amino acids that can be substituted into the peptides of the present invention include, but are not limited to, pyroglutamic acid (pyr), nor-leucine and 3-pyridylalanine.

III. Variations and Modifications of the VEGF Modulators

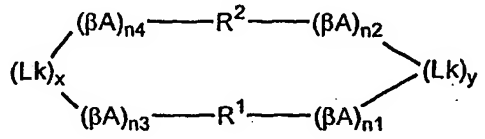
A. Agonist or Antagonist Activity:

Depending on their form, the compounds of the present invention may possess agonist or antagonist activity. The compounds exhibit antagonist activity toward VEGFR-2 when they are in the form of a single peptide chain. Alternatively, the compounds of the invention exhibit agonist activity toward VEGFR-2 when they are in the form of a dimer, i.e., a compound comprised of two peptide chains that may or may not be identical.

B. Dimer Forms:

The compounds of the present invention may be in the form of a dimer. As indicated above, the dimer forms of the present invention possess agonist activity toward VEGFR-2. Preferably, the dimer compounds of the invention have the structure of formula (IV)

(IV)



wherein R^1, R^2, n1, n2, n3, n4, x, y and L_K are defined as follows.

R^1 is a peptide chain that binds to VEGFR-2 and contains a sequence of amino acids of formula (I), (II) or (III) as defined above. R^2 is also a peptide chain that binds to VEGFR-2 and contains a sequence of amino acids of formula (I), (II), or (III). As previously indicated, R^1 and R^2 can be the same or different. It is preferred, however, that R^1 and R^2 are the same.

βA is a β-alanine residue and may or may not be present, meaning that n1, n2, n3 and n4 are independently zero or 1.

Lk is a terminal linking moiety. Each dimer contains only one linking moiety, meaning that one of x and y is zero and the other is 1.

The terminal linking moiety Lk can be any moiety recognized by those skilled in the art as suitable for joining the peptides of R^1 and R^2. Lk is preferably although not necessarily selected from the group consisting of a disulfide bond, a carbonyl moiety and a C_{1-12} linking moiety optionally terminated with one or two -NH- linkages and optionally substituted at one or more available carbon atoms with a lower alkyl substituent. Preferably, the linking moiety comprises -NH-R^3-NH- wherein R^3 is lower (C_{1-6}) alkylene substituted with a functional group such as a carboxyl group or an amino group that enables binding to another molecular moiety (e.g., as may be present on the surface of a solid support), and is optionally substituted with a lower alkyl group. Optimally, the linking moiety is a lysine residue or lysine amide, i.e., a lysine residue wherein the carboxyl group has been converted to an amide moiety -$CONH_2$.

C. DISULFIDE BONDS:

When a pair of cysteine residues is present within a peptide of the invention, it is preferred that the pair form a disulfide bond linking these residues. The disulfide bond may be present within a single peptide chain forming an intramolecular disulfide bond. Alternatively, if the compound includes an additional cysteine-containing peptide chain, the disulfide bond may connect the two chains. In addition, where an additional pair of cysteine residues exists in the compound, more than one disulfide bond may be present.

D. N-TERMINAL MODIFICATIONS:

One can also modify the amino terminus of the peptide to produce other compounds of the invention. Amino terminal modifications include methylation (i.e., conversion of a free amino group to an $-NHCH_3$ or $-N(CH_3)_2$ moiety), acetylation (with either acetic acid *per se*, or with a halogenated derivative thereof such as α-chloroacetic acid, α-bromoacetic acid, or α-iodoacetic acid), addition of a benzyloxycarbonyl group, or blocking with a blocking group containing a carboxylate functionality RCOO- or a sulfonyl functionality $R-SO_2-$, where R is selected from the group consisting of alkyl, aryl, heteroaryl, alkyl aryl, and the like, and similar groups. One can also incorporate a desamino residue at the N-terminus, so that there is no terminal amino group, to decrease susceptibility to proteases or to restrict the conformation of the peptide chain.

Particularly preferred amino terminal modifications herein include conjugation to a polyethylene glycol molecule ("PEGylation") and acetylation. When N-terminal modification is desired, it is also preferred that the peptide chains contain no amino groups other than at the N-terminus (and thus no lysine residues), so that N-terminal-specific modification may be carried out.

(i) PEGYLATED COMPOUNDS

The peptides and compounds of the invention can advantageously be modified with or covalently coupled to one or more of a variety of hydrophilic polymers. It has been found that when the peptide compounds are derivatized with a hydrophilic polymer, their solubility and circulation half-lives are increased and their immunogenicity is masked. Quite surprisingly, the foregoing can be accomplished with little, if any, diminishment in binding activity. Nonproteinaceous polymers suitable for use in accordance with the present invention include, but are not limited to, polyalkylethers as exemplified by polyethylene glycol and polypropylene glycol, polylactic acid, polyglycolic acid, polyoxyalkenes, polyvinylalcohol, polyvinylpyrrolidone, cellulose and cellulose derivatives, dextran and dextran derivatives, etc. Generally, such hydrophilic polymers have an average molecular weight ranging from about 500 to about 100,000 daltons, more preferably from about 2,000 to about 60,000 daltons and, even more preferably, from about 5,000 to about 50,000 daltons. In preferred embodiments, such hydrophilic

polymers have average molecular weights of about 5,000 daltons, 10,000 daltons 20,000 daltons and 40,000 daltons.

The peptide compounds of the invention can be derivatized with or coupled to such polymers using any of the methods set forth in Zallipsky (1995) *Bioconjugate Chem.* 6:150-165; Monfardini et al. (1995) *Bioconjugate Chem.* 6:62-69; U.S. Patent No. 4,640,835; U.S. Patent No. 4,496,689; U.S. Patent No. 4,301,144; U.S. Patent No. 4,670,417; U.S. Patent No. 4,791,192; U.S. Patent No. 4,179,337 or WO 95/34326.

In a preferred embodiment, the N-terminus of a peptide of the invention is coupled to a polyethylene glycol molecule. It is particularly preferred that the polymer is selected from the group consisting of polyethylene glycol, polypropylene glycol, polylactic acid, polyglycolic acid and derivatives thereof. Most preferably the polymer is polyethylene glycol (PEG), in which case the peptide is referred to as "PEGylated." PEG is a linear, water-soluble polymer of ethylene oxide repeating units with two terminal hydroxyl groups. PEGs are classified by their molecular weights which typically range from about 500 daltons to about 40,000 daltons. In a presently preferred embodiment, the PEGs employed have an average molecular weight of from about 500 to about 80,000 daltons. It is particularly preferred that the polymer has an average molecular weight of between about 5,000 to 40,000 daltons. Preferred PEGylated compounds include, by way of example, the following:

(PEG_{10K})-ERVTTC(1-Nal)PGEYGGVECYSVAY (SEQ ID NO: 114);
(PEG_{10K})-RVTTC(1-Nal)PGEYGGVECYSVAY (SEQ ID NO: 113); and
(PEG_{5K})-ERVTTC(1-Nal)PGEYGGVECYSVAY (SEQ ID NO: 114).

The PEG coupled to the peptide compounds of the invention can be either branched or unbranched. (See, e.g. Monfardini et al. (1995) *Bioconjugate Chem.* 6:62-69.) PEG is commercially available from Shearwater Polymers, Inc. (Huntsville, Alabama), Sigma Chemical Co. and other companies. Suitable PEGs include, but are not limited to, monomethoxypolyethylene glycol (MePEG-OH), monomethoxypolyethylene glycol-succinate (MePEG-S), monomethoxypolyethylene glycol-succinimidyl succinate (MePEG-S-NHS), monomethoxypolyethylene glycol-amine (MePEG-NH_2),

monomethoxypolyethylene glycol-tresylate (MePEG-TRES) and monomethoxypolyethylene glycol-imidazolyl-carbonyl (MePEG-IM).

Briefly, in one exemplary embodiment, the hydrophilic polymer that is employed, e.g., PEG, is capped at one terminus by an unreactive group such as a methoxy or ethoxy group. Thereafter, the polymer is activated at the other terminus by reaction with a suitable activating agent, such as a cyanuric halide (e.g., cyanuric chloride, bromide or fluoride), diimidazole, an anhydride reagent (e.g., a dihalosuccinic anhydride, such as dibromosuccinic anhydride), acyl azide, *p*-diazoniumbenzyl ether, 3-(*p*-diazoniumphenoxy)-2-hydroxypropylether, or the like. The activated polymer is then reacted with a peptide compound of the invention to produce a polymer-derivatized peptide compound. Alternatively, a functional group in the peptide compounds of the invention can be activated for reaction with the polymer, or two groups can be joined in a concerted coupling reaction using known coupling methods. It will be readily appreciated that the peptide compounds of the invention can be derivatized with PEG using a myriad of other reaction schemes known to those of skill in the art.

(ii) ACETYLATED COMPOUNDS

In some instances, the N-terminus of the peptide is acetylated. A preferred acetylated peptide is as follows:

Ac-ERVTTCWPGEYGGVECYSVAY (SEQ ID NO: 105).

The peptides and compounds of the invention can be modified with an acetyl moiety (Ac) using standard techniques known to those skilled in the art. On such technique includes combining the peptide with an acetylating reagent (e.g., acetyl chloride, acetic anhydride) in a suitable solvent to form the acetylated product. To the extent that other acetylated products are formed during the reaction, the N-terminus derivative can be isolated using conventional separation techniques.

E. C-TERMINAL MODIFICATIONS:

The peptides and compounds of the invention can advantageously be modified to include an amide functionality at the carboxyl terminus of the peptide. Preferred amidated peptides include:

RVTTCWPGEYGGVECYSVKY(NH_2) (SEQ ID NO: 95); and
ERVTTCWPGEYGGVECYSVAY(NH_2) (SEQ ID NO: 105).

In preparing peptides wherein the C-terminus carboxyl group is replaced by the amide -C(O)NR^3R^4 where R^3 and R^4 are independently H or lower (C_{1-6}) alkyl, a benzhydrylamine resin is preferably used as the solid support for peptide synthesis. Upon completion of the synthesis, a hydrogen fluoride treatment is employed to release the peptide from the support, directly resulting in the free peptide amide (i.e., the C-terminus is -C(O)NH_2). Alternatively, use of a chloromethylated resin during peptide synthesis coupled with reaction with ammonia (to cleave the side chain protected peptide from the support) yields the free peptide amide and reaction with an alkylamine or a dialkylamine yields a side chain protected alkylamide or dialkylamide (i.e., the C-terminus is -C(O)NR^3R^4 where R^3 and R^4 are as defined above). Side chain protecting groups are then removed in the usual fashion by treatment with hydrogen fluoride to give the free amides, alkylamides, or dialkylamides.

F. OTHER MODIFICATIONS:

One can also replace the naturally occurring side chains of the 20 genetically encoded amino acids (or the stereoisomeric D amino acids) with other side chains, for instance with groups such as alkyl, lower alkyl, cyclic 4-, 5-, 6- or 7-membered alkyl, amide, amide lower alkyl, amide di(lower alkyl), lower alkoxy, hydroxy, carboxy and the lower ester derivatives thereof, and 4-, 5-, 6- or 7-membered heterocyclic. In particular, proline analogues in which the ring size of the proline residue is changed from 5 members to 4, 6, or 7 members can be employed.

One can also readily modify the peptides herein by phosphorylation or other methods as described in Hruby et al. (1990) *Biochem J.* 268:249-262. Thus, the peptides of the invention also serve as structural models for non-peptidic compounds with similar

biological activity. For example, the peptide backbones may be replaced with a backbone composed of phosphonates, amidates, carbamates, sulfonamides, secondary amines, and N-methylamino acids.

IV. UTILITY

The compounds of the invention are useful *in vitro* as unique tools for understanding the biological role of vascular endothelial cell growth factor, including the evaluation of the many factors thought to influence, and be influenced by, the production of vascular endothelial cell growth factor and the binding of vascular endothelial cell growth factor to the VEGFR-2 (e.g., the mechanism of endothelial cell growth factor signal transduction/receptor activation). The present compounds are also useful in the development of other compounds that bind to VEGFR-2, because the compounds provide important structure-activity relationship (SAR) information that facilitates that development.

Moreover, based on the ability to bind to VEGFR-2 and related receptors, a compound of the invention can be used as a reagent for detecting a VEGFR-2 receptor or related receptor on living cells, fixed cells, in biological fluids, in tissue homogenates, in purified, natural biological materials, etc. For example, by labeling a compound of the invention, one can identify a cell expressing VEGFR-2 on its surface. In addition, based on its ability to bind to VEGFR-2, a compound of the invention can be used in *in situ* staining, FACS (fluorescence-activated cell sorting), Western blotting, ELISA (enzyme-linked immunoadsorptive assay), etc. or in receptor purification or in purifying cells expressing VEGFR-2 on the cell surface (or inside permeabilized cells).

A compound of the invention can also be utilized as a commercial research reagent for various medical research and diagnostic uses. Such uses include but are not limited to: (1) use as a calibration standard for quantitating the activities of candidate VEGFR-2 antagonists in a variety of functional assays; (2) use as a blocking reagent in random peptide screening, i.e., in searching for new families of VEGFR-2 peptide ligands; (3) use in the co-crystallization with VEGFR-2, i.e., a compound of the invention will allow formation of crystals bound to VEGFR-2, enabling the determination of receptor/peptide structure x-ray crystallography; (4) use in inhibiting or decreasing the proliferation and growth of vascular endothelial cell growth factor-dependent cell lines,

such as human umbilical vein endothelial cells (HUVEC); and (5) other research and diagnostic applications wherein the VEGFR-2 is antagonized and such antagonization is conveniently calibrated against a known quantity of a vascular endothelial cell growth factor antagonist, and the like.

A particularly preferred application for the compounds of the present invention is in imaging and assessing neovascularization during angiogenesis. Although not wishing to be bound by theory, the expression of the VEGFR-2 in endothelial tissue and its reported concentration increase during angiogenesis may allow the compounds of the invention to be useful in imaging, and thereby assessing, neovascularization associated with several disorders including cancer. There are numerous means by which the compounds of the invention may serve as sensitive and specific imaging agents for angiogenesis. For example:

a) A compound of the invention can be labeled with a radionuclide such as ^{99m}Tc, ^{111}In or ^{123}I and injected intravenously into the patient. Either 3-D single photon emission computed tomography (SPECT) imaging or 2-D planar gamma scintigraphy can be applied to localize tracer concentration that positively correlates with neovascularization. There are numerous labeling mechanisms for the metals which would generally include either the use of bifunctional chelators or amino acid derived chelators. In addition, labels such as ^{123}I can be attached via a covalent bond to the compound.

b) A compound of the invention can be labeled with a positron-emitting isotope such as ^{11}C, ^{18}F, ^{68}Ga, ^{76}Br, ^{61}Cu, or ^{64}Cu, injected into the patient and imaged using positron-emitting tomography (PET). PET provides improved sensitivity and resolution compared with SPECT, although the availability of PET isotopes is lower as compared to the radionuclides used for SPECT.

c) A compound of the invention can be PEGylated and labeled with one of the above positron-emitting nuclei or gamma-emitting radionuclides to extend blood half life and reduce extravasation.

d) A compound of the invention can be attached to a liposome or amorphous polymer to reduce extravasation. The carrier (i.e. liposome or polymer) is then labeled with one or more of the above positron-emitting atoms or gamma-emitting radionuclides for detection with PET or SPECT. The longer-lived nuclei such as ^{111}In or ^{76}Br are most appropriate as there could be significant delay between tracer administration and imaging

while waiting for the unbound compound to be eliminated from the bloodstream. The carrier can also be labeled with multiple copies of paramagnetic nuclei such as Gd, Fe or Mn for detection with magnetic resonance imaging (MRI). Although MRI sensitivity of tracer detection is relatively low (particularly when compared to SPECT or PET), spatial resolution is improved. In addition, MRI techniques have the added benefit of avoiding the use of ionizing radiation.

e) A compound of the invention can be attached to a monocrystalline iron oxide (MION) particle and used for detection via MRI.

f) A compound of the can be labeled with a fluorophore that preferentially emits in the near infrared region (700-1000nm) and used for the detection of angiogenesis in tissue relatively close to the surface of the skin.

Accordingly, the invention provides a method for imaging and assessing neovascularization during angiogenesis comprising the steps of administering a compound of the present invention to a patient wherein the compound is coupled to a detectable label to form a labeled compound, allowing the labeled compound to bind to VEGFR-2, and detecting the detectable label. It is preferred that the detectable label is selected from the group consisting of ^{99m}Tc, ^{111}In, ^{123}I, ^{11}C, ^{18}F, ^{68}Ga, ^{76}Br, ^{61}Cu, ^{64}Cu, Gd, Fe, Mn and a fluorophore. It is also preferred that the detecting step is performed using SPECT, 2-D planar gamma scintigraphy, PET, MRI, infrared detection, or a combination thereof.

An antagonist compound of the invention can also be administered to a warm blooded animal, including a human, to treat a disease, condition or disorder that is responsive to a compound that antagonizes the effects of vascular endothelial cell growth factor *in vivo*. Thus, the present invention encompasses methods for treating a patient who would benefit from administration of a VEGFR-2 antagonist, comprising administering to the patient a therapeutically effective amount of a VEGFR-2 antagonist and thus alleviate the symptoms associated with angiogenesis *in vivo*. For example, an antagonist compound of this invention will find use in the treatment of diseases such as psoriasis, rheumatoid arthritis, retinopathy and cancer.

Alternatively, an agonist compound of the invention can be administered to a warm blooded animal, including a human, to treat a disease, condition or disorder that is responsive to a compound that agonizes the effects of vascular endothelial cell growth factor *in vivo*. Thus, the present invention encompasses methods for treating a patient who

would benefit from administration of a VEGFR-2 agonist and thus alleviate the symptoms associated with decreased angiogenesis *in vivo*. For example, an agonist compound of this invention will find use in the treatment of diseases such as coronary artery disease wherein the formation of new blood vessels serving cardiac tissue at least partially remedies the decrease in blood flow from coronary vessels that are obstructed.

Accordingly, the invention includes pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of the invention in association with a pharmaceutical carrier or diluent. The composition can be administered by oral, parenteral (intramuscular, intraperitoneal, intravenous (IV) or subcutaneous) injection, transdermal (either passively or using iontophoresis or electroporation), or transmucosal (nasal, vaginal, rectal, or sublingual) routes of administration, or using bioerodible inserts, and can be formulated in dosage forms appropriate for each route of administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, an additional substance other than an inert diluent, e.g., a lubricating agent such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise a buffering agent. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions and syrups, with the elixirs containing an inert diluent commonly used in the art, such as water. These compositions can also include one or more adjuvants, such as a wetting agent, an emulsifying agent, a suspending agent, a sweetening agent, a flavoring agent or a perfuming agent.

Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain one or more adjuvants such as a preserving agent, a wetting agent, an emulsifying agent and a dispersing agent. The dosage forms may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions.

They can also be manufactured using sterile water, or some other sterile injectable medium, prior to use.

Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, an excipient such as cocoa butter or a suppository wax. Compositions for nasal or sublingual administration are also prepared with one or more standard excipients well known in the art.

The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient is such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, the route of administration, the duration of the treatment desired, and other factors well known to those skilled in the art. Generally, dosage levels of between 0.001 to 10 mg/kg of body weight daily are administered to mammals.

It is to be understood that while the invention has been described in conjunction with the preferred specific embodiments thereof, that the foregoing description as well as the examples which follow are intended to illustrate and not limit the scope of the invention. Other aspects, advantages and modifications within the scope of the invention will be apparent to those skilled in the art to which the invention pertains.

EXPERIMENTAL

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to prepare and use the compounds disclosed and claimed herein. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.) but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in °C and pressure is at or near atmospheric.

Solid phase reactions were carried out at room temperature. Unless otherwise indicated, all starting materials and reagents were obtained commercially, e.g., from Aldrich, Sigma and ICN, and used without further purification.

Also, in these examples and throughout this specification, the abbreviations employed have their generally accepted meanings, as follows:

Ac = acetyl
Alloc = allyloxycarbonyl

Boc = *t*-butoxycarbonyl
Cbz = benzyloxycarbonyl
DMF = dimethyl formamide
Fmoc = fluorenylmethyl oxycarbonyl
HBTU = O-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
Pyr = pyroglutamic acid

EXAMPLES 1-8

VEGF COMPETITION ASSAYS

The peptides of Table 1 were synthesized chemically using standard solid phase techniques as described above. To evaluate binding affinity, the synthesized peptides were tested against labeled VEGF by competing for binding to VEGFR-2 in a standard scintillation proximity assay (STND SPA). Briefly stated, the binding portion of human VEGFR-2 is replicated and thereafter attached to a suitable substrate using conventional techniques. A known amount of peptide is introduced together with a standard amount of ^{125}I labeled VEGF (^{125}I-VEGF-165 available from Amersham Pharmacia Biotech, Piscataway, New Jersey). After a sufficient period of time to allow for binding, the substrate is washed and a scintillation detector is used to detect ^{125}I labeled VEGF. If scintillation is detected, the quantity of peptide used is not sufficient to displace the ^{125}I labeled VEGF. Alternatively, if no scintillation is detected, the quantity of peptide used is sufficient to remove the ^{125}I labeled VEGF. By testing a series of dilutions of the peptide, it is possible to determine the minimum amount of peptide necessary to remove ^{125}I labeled VEGF. The procedure is then repeated for a different peptide. In this way, it is possible to determine the relative binding affinities for each peptide. Some peptides were also tested in a mouse VEGFR-2 based SPA (Mouse SPA). The testing procedure is substantially the same as that described immediately above with the exception that mouse-derived VEGFR-2 is substituted for human VEGFR-2.

In addition, some peptides were tested for inhibiting the proliferation of human umbilical vein endothelial cells (HUVEC). By way of general procedure, human umbilical vein endothelial cells are placed on a suitable culture medium. A standard amount of VEGF along with a known amount of peptide is added to the cells. After a sufficient period of time, the cultures are inspected for detection of cell proliferation. If cell proliferation is detected, the quantity of peptide used is not sufficient to displace VEGF

and consequently inhibit cell growth. Alternatively if no proliferation is detected, the quantity of peptide used is sufficient to inhibit VEGF-induced proliferation of cells. By testing a series of dilutions, it is possible to determine the minimum amount of peptide necessary to inhibit VEGF-induced proliferation of human umbilical vein endothelial cells (HUVEC). The procedure is then repeated for a different peptide. In this way, it is possible to determine the relative inhibitory effect for each peptide.

The peptides, along with their corresponding IC_{50} values (in nM) for standard SPA (STND SPA), HUVEC and Mouse SPA, are shown in Table 1. The results of these assays reveal important information about the structure-activity relationship for VEGF to its receptor.

Table 1

Ex. No.	Sequence	STND SPA	HUVEC	Mouse SPA
1	REECYTNAAGVLECWVS (SEQ ID NO: 75)	128000	-	-
2	ERVISCWPGEYGGVECWTVNL (SEQ ID NO: 64)	380	-	34000
3	SGDVACWPSEYGGVECWSLHY (SEQ ID NO: 67)	52	-	16000
4	DGVVSCWPSEYGGEDCFNLHY (SEQ ID NO: 81)	19.2	-	1700
5	MRVEYCWPAEYGGVECFSPRD (SEQ ID NO: 86)	35	-	19000
6	TQVESCWPGEYGGVECWKLRY (SEQ ID NO: 80)	52	-	15000
7	KRVVSCWPGEYGGVECYNVKY (SEQ ID NO: 79)	1.27	2100	40000
8	ERVTTCWPGEYGGVECYSVKY (SEQ ID NO: 77)	0.86	390	14000

"-" denotes assay not performed.

EXAMPLES 9-13

N-TERMINAL TRUNCATIONS

The peptides of Table 2, each based on the sequence ERVTTCWPGEYGGVECYSVKY (SEQ ID NO: 77), were synthesized chemically using standard solid phase techniques as described *infra*. As seen below, each peptide is the result of effectively deleting the amino acid located on the N-terminus of the peptide in a sequential fashion.

The peptides were tested as described above for Examples 1-8. The peptides along with their corresponding IC_{50} values (in nM) for standard SPA (STND SPA) and HUVEC are shown in Table 2. The results of these assays reveal important information about the structure-activity relationship for VEGF to its receptor.

Table 2

Ex. No.	Sequence	STND SPA	HUVEC
9	RVTTCWPGEYGGVECYSVKY (SEQ ID NO: 95)	0.76	1280
10	VTTCWPGEYGGVECYSVKY (SEQ ID NO: 96)	3.70	1830
11	TTCWPGEYGGVECYSVKY (SEQ ID NO: 97)	44.00	-
12	TCWPGEYGGVECYSVKY (SEQ ID NO: 98)	79.00	-
13	CWPGEYGGVECYSVKY (SEQ ID NO: 162)	12600	-

"-" denotes assay not performed.

EXAMPLES 14-17

C-TERMINAL TRUNCATIONS

The peptides of Table 3, each based on the sequence RVTTCWPGEYGGVECYSVKY (SEQ ID NO: 95), were synthesized chemically using standard solid phase techniques as described previously. As seen in Table 3, each peptide is the result of effectively deleting the amino acid located on the C-terminus of the peptide in a sequential fashion.

The peptides were tested as described above for Examples 1-8. The peptides along with their corresponding IC_{50} values (in nM) for standard SPA (STND SPA) are

shown below. Again, the results of these assays reveal important information about the structure-activity relationship for VEGF to its receptor.

Table 3

Ex. No.	Sequence	STND SPA
14	RVTTCWPGEYGGVECYSVK (SEQ ID NO: 99)	440
15	RVTTCWPGEYGGVECYSV (SEQ ID NO: 100)	360
16	RVTTCWPGEYGGVECYS (SEQ ID NO: 163)	>25000
17	RVTTCWPGEYGGVECY (SEQ ID NO: 164)	>25000

EXAMPLES 18-23

LYSINE (K) SUBSTITUTIONS

The peptides of Table 4 were synthesized chemically using standard solid phase techniques as described previously. The amino acid lysine, however, was substituted for other amino acids.

The peptides were tested as described above for Examples 1-8. The peptides along with their corresponding IC_{50} values (in nM) for standard SPA (STND SPA), HUVEC and Mouse SPA are shown below. Again, the results of these assays reveal important information about the structure-activity relationship for VEGF to its receptor.

Table 4

Ex. No.	Sequence	STND SPA	HUVEC	Mouse SPA
18	ERVTTCWPGEYGGVECYSVK(alloc)Y (SEQ ID NO: 101)	0.45	380	3300
19	RVTTCWPGEYGGVECYSVK(alloc)Y (SEQ ID NO: 102)	0.92	1240	-
20	ERVTTCWPGEYGGVECYSVRY (SEQ ID NO: 103)	0.36	380	-
21	RVTTCWPGEYGGVECYSVRY (SEQ ID NO: 104)	0.62	1690	-
22	ERVTTCWPGEYGGVECYSVAY (SEQ ID NO: 105)	0.57	500	3600
23	RVTTCWPGEYGGVECYSVAY (SEQ ID NO: 106)	1.00	1170	-

"-" denotes assay not performed.

EXAMPLES 24-25

C-TERMINAL AMIDATION

The peptides of Table 5 based were synthesized chemically using standard solid phase techniques as described previously. In addition, the C-terminus of each peptide was amidated using techniques well known to those skilled in the art.

The peptides were tested as described above for Examples 1-8. The peptides along with their corresponding IC_{50} values (in nM) for standard SPA (STND SPA) and HUVEC are shown below. As before, the results of these assays reveal important information about the structure-activity relationship for VEGF to its receptor.

Table 5

Ex. No.	Sequence	STND SPA	HUVEC
24	RVTTCWPGEYGGVECYSVKY(NH_2) (SEQ ID NO: 95)	5.8	-
25	ERVTTCWPGEYGGVECYSVAY (SEQ ID NO: 105)	3.9	15000

"-" denotes assay not performed.

EXAMPLE 26

N-TERMINAL ACETYLATION

The following peptide was synthesized chemically using standard solid phase techniques as described previously. In addition, the N-terminus of the peptide was acetylated using techniques well known to those skilled in the art.

The peptide was tested as described above for Examples 1-8. The peptide along with its corresponding IC_{50} value (in nM) for standard SPA (STND SPA) is shown below. The results of the assay reveals important information about the structure-activity relationship for VEGF to its receptor.

Table 6

Ex. No.	Sequence	STND SPA
26	Ac-ERVTTCWPGEYGGVECYSVAY (SEQ ID NO: 105)	0.59

EXAMPLES 27-31

TRYPTOPHAN (W) SUBSTITUTIONS

The peptides of Table 7 were synthesized chemically using standard solid phase techniques as described previously. The amino acid tryptophan, however, was substituted for other amino acids.

The peptides were tested as described above for Examples 1-8. The peptides along with their corresponding IC_{50} values (in nM) for standard SPA (STND SPA), HUVEC and Mouse SPA are shown in Table 7. Again, the results of these assays reveal important information about the structure-activity relationship for VEGF to its receptor.

Table 7

Ex. No.	Sequence	STND SPA	HUVEC	Mouse SPA
27	RVTTC(1-Nal)PGEYGGVECYSVKY (SEQ ID NO: 107)	0.63	1090	4700
28	RVTTC(2-Nal)PGEYGGVECYSVKY (SEQ ID NO: 108)	4.50	-	-
29	RVTTCFPGEYGGVECYSVAY (SEQ ID NO: 109)	25.00	-	-
30	RVTTC(1-Nal)PGEYGGVECYSVAY (SEQ ID NO: 113)	1.39	-	-
31	ERVTTC(1-Nal)PGEYGGVECYSVAY (SEQ ID NO: 114)	0.59	-	-

"-" denotes assay not performed.

EXAMPLES 32-34

ARGININE (R) SUBSTITUTIONS

The peptides of Table 8 were synthesized chemically using standard solid phase techniques as described previously. The amino acid arginine, however, was substituted for other amino acids.

The peptides were tested as described above for Examples 1-8. The peptides along with their corresponding IC_{50} values (in nM) for standard SPA (STND SPA) and

HUVEC are shown below. The results of these assays reveal important information about the structure-activity relationship for VEGF to its receptor.

Table 8

Ex. No.	Sequence	STND SPA	HUVEC
32	HVTTCWPGEYGGVECYSVRY (SEQ ID NO: 110)	1.07	730
33	GVTTCWPGEYGGVECYSVRY (SEQ ID NO: 111)	2.20	1610
34	(Pyr)VTTCWPGEYGGVECYSVRY (SEQ ID NO: 112)	0.99	460

EXAMPLES 35-44

ALANINE SCAN

The peptides of Table 9, each based on the sequence RVTTCWPGEYGGVECYSVAY (SEQ ID NO: 106), were synthesized chemically using standard solid phase techniques as described previously. As seen below, the amino acid alanine replaces one amino acid within each peptide.

The peptides were tested as described above for Examples 1-8. The peptides along with their corresponding IC_{50} values (in nM) for standard SPA (STND SPA) and HUVEC are shown below. The results of these assays reveal important information about the structure-activity relationship for VEGF to its receptor.

Table 9

Ex. No.	Sequence	STND SPA	HUVEC
35	RVTTCWPGEYGGVECYSVAY (SEQ ID NO: 106)	1.00	1120*
36	RVATCWPGEYGGVECYSVAY (SEQ ID NO: 115)	6.30	-
37	RVTACWPGEYGGVECYSVAY (SEQ ID NO: 116)	1.30	780
38	RVTTCAPGEYGGVECYSVAY (SEQ ID NO: 117)	3000.00	-
39	RVTTCWPGAYGGVECYSVAY (SEQ ID NO: 118)	5.00	-
40	RVTTCWPGEAGGVECYSVAY (SEQ ID NO: 119)	171.00	-
41	RVTTCWPGEYGGVACYSVAY (SEQ ID NO: 120)	43.00	-
42	RVTTCWPGEYGGVECASVAY (SEQ ID NO: 121)	920.00	-
43	RVTTCWPGEYGGVECYAVAY (SEQ ID NO: 122)	2.00	3300
44	RVTTCWPGEYGGVECYSVRA (SEQ ID NO: 123)	230.00	-

"-" denotes assay not performed.

* While not identical with the result of experiment 23, this HUVAC assay value is sufficiently comparable.

EXAMPLES 45-47

PEGYLATION

The compounds of Table 10 were synthesized using standard solid phase techniques described above.

The peptides were tested as described above for Examples 1-8. The peptides along with their corresponding IC_{50} values (in nM) for standard SPA (STND SPA) are shown below. The results of these assays reveal important information about the structure-activity relationship for VEGF to its receptor. These PEGylated compounds are also expected to exhibit improved pharmacokinetic values e.g., serum half-life, bioavailablity, etc.

Table 10

Ex. No.	Sequence	SPA IC_{50}
45	(PEG_{10K})-ERVTTC(1-Nal)PGEYGGVECYSVAY (SEQ ID NO: 114)	5.40
46	(PEG_{10K})-RVTTC(1-Nal)PGEYGGVECYSVAY (SEQ ID NO: 113)	10.80
47	(PEG_{5K})-ERVTTC(1-Nal)PGEYGGVECYSVAY (SEQ ID NO: 114)	1.82

The compounds of the invention are thus ligands for VEGFR-2. In addition, the compounds of the invention demonstrate effective antagonism for the VEGFR-2.

EXAMPLE 48

IMAGING ANGIOGENESIS

^{123}I is covalently attached to a compound of the invention using a conventional technique. The labeled compound is administered intravenously to a cancer patient in an amount sufficient to detect neovascularization in the patient's tumor. After a sufficient time has passed to allow for clearance of unbound labeled compound, the tumor-affected area is imaged using three-dimensional single photon emission computed tomography. A concentrated area of labeled-compound is detected indicating the presence of new blood vessels in the patient's tumor. In response, the patient's chemotherapy regimen is adjusted accordingly.

CLAIMS

1. A compound comprising a peptide chain approximately 15 to 40 amino acids in length that binds to VEGFR-2 and contains a sequence of amino acids of formula (I)

(I) $X_1CX_2X_3X_4X_5X_6GX_7X_8X_9CX_{10}X_{11}X_{12}$ (SEQ ID NO: 1)

wherein each amino acid is indicated by standard one-letter abbreviation, and wherein X_1 is S, T, Y, A, Q, V or E; X_2 is W, R, Y, G, Q, F or A; X_3 is P, L, T, S, A or E; X_4 is G, S, A or N; X_5 is E, D or A; X_6 is Y, F, N or A; X_7 is G or V; X_8 is V, E, F, L or M; X_9 is E, D, V or A; X_{10} is W, Y, F or A; X_{11} is S, A, E, G, T, W, V, N, K or F; and X_{12} is L, H, R, P, Q, V, M, S or I.

2. The compound of claim 1, wherein the sequence of amino acids is selected from the group consisting of:

SCWPGEYGGVECWSL (SEQ ID NO: 4);
SCWLGEYGGEECWSH (SEQ ID NO: 5);
TCWSGEYGGVECWAR (SEQ ID NO: 6);
SCWPGDFGGVECWSL (SEQ ID NO: 7);
YCWPGEYGGVDCWSP (SEQ ID NO: 8);
SCWAGEYGGVECWSQ (SEQ ID NO: 9);
ACWTGEYGGEECWEL (SEQ ID NO: 10);
TCWPGEYGGVECWAV (SEQ ID NO: 11);
TCWPGEYGGVECWGR (SEQ ID NO: 12);
SCWPGEYGGVECWTV (SEQ ID NO: 13);
TCWPGEYGGVECWSL (SEQ ID NO: 14);
SCWEGDNGGVECWWL (SEQ ID NO: 15);
ACWPSEYGGVECWSL (SEQ ID NO: 16);
SCWPGEFGGVECWSV (SEQ ID NO: 17);
QCWPGDYGGVDCWSV (SEQ ID NO: 18);
TCWPGEYGGEECWSL (SEQ ID NO: 19);
SCWPGEFGGFDCWSM (SEQ ID NO: 20);
YCRPGEYGGEECWSL (SEQ ID NO: 21);

SCWPAEYGGVECWSM (SEQ ID NO: 22);
SCWPGEYGGEECYWL (SEQ ID NO: 23);
ECYTNAAGVLECWVS (SEQ ID NO: 24);
TCWPGEYGGEECWSI (SEQ ID NO: 25);
TCWPGEYGGVECYSV (SEQ ID NO: 26);
SCWPGEYGGEECWSL (SEQ ID NO: 27);
SCWPGEYGGVECYNV (SEQ ID NO: 28);
SCWPGEYGGVECWKL (SEQ ID NO: 29);
SCWPSEYGGEDCFNL (SEQ ID NO: 30);
TCWPGEYGGEVCWAL (SEQ ID NO: 31);
SCWPGEYGGVDCWSV (SEQ ID NO: 32);
SCWPGEYGGVECWTL (SEQ ID NO: 33);
YCWPAEYGGVECFSP (SEQ ID NO: 34);
ACGPGEYGGEECWFV (SEQ ID NO: 35);
SCWTGEYGGVECWTL (SEQ ID NO: 36);
SCWPGEYGGEVCWSL (SEQ ID NO: 37);
VCWPGEYGGVECWNV (SEQ ID NO: 38);
SCQPGEYGGMVCWSL (SEQ ID NO: 39);
VCWPGEYGGEDCWSL (SEQ ID NO: 40);
SCFPSEYGGEDCWSL (SEQ ID NO: 41);
SCWEGEYGGVECWSI (SEQ ID NO: 42);
TC(1-Nal)PGEYGGVECYSV (SEQ ID NO: 43);
TC(2-Nal)PGEYGGVECYSV (SEQ ID NO: 44);
TCFPGEYGGVECYSV (SEQ ID NO: 45);
ACWPGEYGGVECYSV (SEQ ID NO: 46);
TCAPGEYGGVECYSV (SEQ ID NO: 47);
TCWPGAYGGVECYSV (SEQ ID NO: 48);
TCWPGEAGGVECYSV (SEQ ID NO: 49);
TCWPGEYGGVACYSV (SEQ ID NO: 50);
TCWPGEYGGVECASV (SEQ ID NO: 51); and
TCWPGEYGGVECYAV (SEQ ID NO: 52).

3. The compound of claim 2, wherein the sequence of amino acids is selected from the group consisting of:

SREVSCWPGEYGGVECWSLKE (SEQ ID NO: 53);
ARVVSCWPGEYGGVECWSLNS (SEQ ID NO: 54);
PGVVSCWLGEYGGEECWSHNY (SEQ ID NO: 55);
FPLVSCWPGEYGGVECWSLKT (SEQ ID NO: 56);
TGVVTCWSGEYGGVECWARNT (SEQ ID NO: 57);
HRVDSCWPGDFGGVECWSLSE (SEQ ID NO: 58);
VRVEYCWPGEYGGVDCWSPKP (SEQ ID NO: 59);
HQVVSCWAGEYGGVECWSQNA (SEQ ID NO: 60);
NRVEACWTGEYGGEECWELNL (SEQ ID NO: 61);
AGQVTCWPGEYGGVECWAVKY (SEQ ID NO: 62);
VTCWPGEYGGVECWGRKG (SEQ ID NO: 63);
ERVISCWPGEYGGVECWTVNL (SEQ ID NO: 64);
SRVVTCWPGEYGGVECWSLEL (SEQ ID NO: 65);
NRVESCWEGDNGGVECWWLKY (SEQ ID NO: 66);
SGDVACWPSEYGGVECWSLHY (SEQ ID NO: 67);
HWEGSCWPGEFGGVECWSVNY (SEQ ID NO: 68);
DRMQQCWPGDYGGVDCWSVDL (SEQ ID NO: 69);
HRVVTCWPGEYGGEECWSLGE (SEQ ID NO: 70);
LDVVSCWPGEFGGFDCWSMKY (SEQ ID NO: 71);
NRVLVCRPGEYGGEECWSLDY (SEQ ID NO: 72);
GGVVSCWPAEYGGVECWSMDY (SEQ ID NO: 73);
GRVESCWPGEYGGEECYWLDS (SEQ ID NO: 74);
REECYTNAAGVLECWVS (SEQ ID NO: 75);
PRVVTCWPGEYGGEECWSIKY (SEQ ID NO: 76);
ERVTTCWPGEYGGVECYSVKY (SEQ ID NO: 77);
EWVVSCWPGEYGGEECWSLKY (SEQ ID NO: 78);
KRVVSCWPGEYGGVECYNVKY (SEQ ID NO: 79);
TQVESCWPGEYGGVECWKLRY (SEQ ID NO: 80);
DGVVSCWPSEYGGEDCFNLHY (SEQ ID NO: 81);
RPSETCWPGEYGGEVCWALKY (SEQ ID NO: 82);

SYVESCWPGEYGGVDCWSVKY (SEQ ID NO: 83);
PRVVSCWPGEYGGVDCWSVKY (SEQ ID NO: 84);
KRAVSCWPGEYGGVECWTLEY (SEQ ID NO: 85);
MRVEYCWPAEYGGVECFSPRD (SEQ ID NO: 86);
SRVLACGPGEYGGEECWFVQY (SEQ ID NO: 87);
ETVESCWTGEYGGVECWTLNY (SEQ ID NO: 88);
VLEVSCWPGEYGGEVCWSLKM (SEQ ID NO: 89);
SRVEVCWPGEYGGVECWNVES (SEQ ID NO: 90);
GPVVSCQPGEYGGMVCWSLNY (SEQ ID NO: 91);
ESDVVCWPGEYGGEDCWSLNY (SEQ ID NO: 92);
GRVVSCFPSEYGGEDCWSLNY (SEQ ID NO: 93);
YQVESCWEGEYGGVECWSIKL (SEQ ID NO: 94);
RVTTCWPGEYGGVECYSVKY (SEQ ID NO: 95);
VTTCWPGEYGGVECYSVKY (SEQ ID NO: 96);
TTCWPGEYGGVECYSVKY (SEQ ID NO: 97);
TCWPGEYGGVECYSVKY (SEQ ID NO: 98);
RVTTCWPGEYGGVECYSVK (SEQ ID NO: 99);
RVTTCWPGEYGGVECYSV (SEQ ID NO: 100);
ERVTTCWPGEYGGVECYSVK(alloc)Y (SEQ ID NO: 101);
RVTTCWPGEYGGVECYSVK(alloc)Y (SEQ ID NO: 102);
ERVTTCWPGEYGGVECYSVRY (SEQ ID NO: 103);
RVTTCWPGEYGGVECYSVRY (SEQ ID NO: 104);
ERVTTCWPGEYGGVECYSVAY (SEQ ID NO: 105);
RVTTCWPGEYGGVECYSVAY (SEQ ID NO: 106);
RVTTC(1-Nal)PGEYGGVECYSVKY (SEQ ID NO: 107);
RVTTC(2-Nal)PGEYGGVECYSVKY (SEQ ID NO: 108);
RVTTCFPGEYGGVECYSVAY (SEQ ID NO: 109);
HVTTCWPGEYGGVECYSVRY (SEQ ID NO: 110);
GVTTCWPGEYGGVECYSVRY (SEQ ID NO: 111);
(Pyr)VTTCWPGEYGGVECYSVRY (SEQ ID NO: 112);
RVTTC(1-Nal)PGEYGGVECYSVAY (SEQ ID NO: 113);
ERVTTC(1-Nal)PGEYGGVECYSVAY (SEQ ID NO: 114);

RVATCWPGEYGGVECYSVAY (SEQ ID NO: 115);
RVTACWPGEYGGVECYSVAY (SEQ ID NO: 116);
RVTTCAPGEYGGVECYSVAY (SEQ ID NO: 117);
RVTTCWPGAYGGVECYSVAY (SEQ ID NO: 118);
RVTTCWPGEAGGVECYSVAY (SEQ ID NO: 119);
RVTTCWPGEYGGVACYSVAY (SEQ ID NO: 120);
RVTTCWPGEYGGVECASVAY (SEQ ID NO: 121);
RVTTCWPGEYGGVECYAVAY (SEQ ID NO: 122); and
RVTTCWPGEYGGVECYSVRA (SEQ ID NO: 123).

4. The compound of claim 1, in the form of a dimer.

5. The compound of claim 1, containing a disulfide bond.

6. The compound of claim 1, wherein the N-terminus of the peptide is coupled to a polyethylene glycol molecule.

7. The compound of claim 6, wherein the PEGylated peptide is selected from the group consisting of:

(PEG_{10K})-ERVTTC(1-Nal)PGEYGGVECYSVAY (SEQ ID NO: 114);
(PEG_{10K})-RVTTC(1-Nal)PGEYGGVECYSVAY (SEQ ID NO: 113); and
(PEG_{5K})-ERVTTC(1-Nal)PGEYGGVECYSVAY (SEQ ID NO: 114).

8. The compound of claim 1, wherein the N-terminus of the peptide is acetylated.

9. The compound of claim 8, wherein the acetylated peptide is:

Ac-ERVTTCWPGEYGGVECYSVAY (SEQ ID NO: 105).

10. The compound of claim 1, wherein the C-terminus of the peptide is amidated.

11. The compound of claim 10, wherein the amidated peptide is:

RVTTCWPGEYGGVECYSVKY(NH_2) (SEQ ID NO: 95); or

ERVTTCWPGEYGGVECYSVAY(NH_2) (SEQ ID NO: 105).

12. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1 in combination with a pharmaceutically acceptable carrier.

13. A method for treating a patient who would benefit from administration of a VEGFR-2 antagonist, comprising administering to the patient a therapeutically effective amount of a compound comprising a peptide chain approximately 15-40 amino acids in length that binds to VEGFR-2 (KDR) receptor and contains a sequence of amino acids having the structural formula (I)

(I) $X_1CX_2X_3X_4X_5X_6GX_7X_8X_9CX_{10}X_{11}X_{12}$ (SEQ ID NO: 1)

wherein each amino acid is indicated by standard one-letter abbreviation, and wherein X_1 is S, T, Y, A, Q, V or E; X_2 is W, R, Y, G, Q, F or A; X_3 is P, L, T, S, A or E; X_4 is G, S, A or N; X_5 is E, D or A; X_6 is Y, F, N or A; X_7 is G or V; X_8 is V, E, F, L or M; X_9 is E, D, V or A; X_{10} is W, Y, F or A; X_{11} is S, A, E, G, T, W, V, N, K or F; and X_{12} is L, H, R, P, Q, V, M, S or I.

14. The method of claim 13, wherein the patient suffers from a disease selected from the group consisting of psoriasis, rheumatoid arthritis, retinopathy and cancer.

15. A method for imaging and assessing neovascularization during angiogenesis comprising administering a compound of claim 1 to a patient wherein the compound is coupled to a detectable label to form a labeled compound, allowing the labeled compound to bind to VEGFR-2, and detecting the detectable label.

16. The method of claim 15, wherein the detectable label is selected from the group consisting of ^{99m}Tc, ^{111}In, ^{123}I, ^{11}C, ^{18}F, ^{68}Ga, ^{76}Br, ^{61}Cu, ^{64}Cu, Gd, Fe, Mn and a fluorophore.

17. The method of claim 15, wherein the detecting step is performed using SPECT, 2-D planar gamma scintigraphy, PET, MRI, infrared detection, or a combination thereof.

18. A compound comprising a peptide chain approximately 8 to 40 amino acids in length that binds to VEGFR-2 and contains a sequence of amino acids of formula (II)

(II) $CX'_1GX'_2X'_3X'_4CW$ (SEQ ID NO: 2)

wherein each amino acid is indicated by standard one-letter abbreviation, and wherein X'_1 is W or G; X'_2 is P or A; X'_3 is E or D; X'_4 is G or R.

19. The compound of claim 18, wherein the sequence of amino acids is selected from the group consisting of:

CWGPEGCW (SEQ ID NO: 124);
CWGPDGCW (SEQ ID NO: 125);
CGGPEGCW (SEQ ID NO: 126); and
CGGAERCW (SEQ ID NO: 127).

20. The compound of claim 19, wherein the sequence of amino acids is selected from the group consisting of:

SDSVDECWGPEGCWLE (SEQ ID NO: 128);
YNTVENCWGPDGCWLD (SEQ ID NO: 129);
MSLVDKCWGPEGCWLE (SEQ ID NO: 130);
TITVGSCWGPEGCWLDSRY (SEQ ID NO: 131);
IFLGENCWGPDGCWLE (SEQ ID NO: 132);
IREGDMCWGPEGCWVD (SEQ ID NO: 133);
LTLVDNCWGPDGCWLE (SEQ ID NO: 134);
ESRVDDCWGPDGCWLDPIT (SEQ ID NO: 135);
VEYVANCGGAERCWLGTNM (SEQ ID NO: 136);

QDCWGPEGCWLQEQG (SEQ ID NO: 137);
VLDADNCWGPEGCWLE (SEQ ID NO: 138);
MSEVEDCWGPEGCWLE (SEQ ID NO: 139);
NCWGPEGCWLE (SEQ ID NO: 140);
SHRVDDCWGPDGCWLE (SEQ ID NO: 141);
IIEVGNCWGPEGCWLE (SEQ ID NO: 142); and
VDNCWGPEGCWLE (SEQ ID NO: 143).

21. The compound of claim 20, in the form of a dimer.

22. The compound of claim 18, wherein the N-terminus of the peptide is coupled to a polyethylene glycol molecule.

23. The compound of claim 18, wherein the N-terminus of the peptide is acetylated.

24. The compound of claim 18, wherein the C-terminus of the peptide is amidated.

25. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 18 in combination with a pharmaceutically acceptable carrier.

26. A method for treating a patient who would benefit from administration of a VEGFR-2 antagonist, comprising administering to the patient a therapeutically effective amount of a compound comprising a peptide chain approximately 8 to 40 amino acids that binds to VEGFR-2 and contains a sequence of amino acids having the structural formula (II)

(II) $CX'_1GX'_2X'_3X'_4CW$ (SEQ ID NO: 2)

wherein each amino acid is indicated by standard one-letter abbreviation, and wherein X'_1 is W or G; X'_2 is P or A; X'_3 is E or D; X'_4 is G or R.

27. The method of claim 26, wherein the patient suffers from a disease selected from the group consisting of psoriasis, rheumatoid arthritis, retinopathy and cancer.

28. A method for imaging and assessing neovascularization during angiogenesis comprising administering a compound of claim 18 to a patient wherein the compound is coupled to a detectable label to form a labeled compound, allowing the labeled compound to bind to VEGFR-2, and detecting the detectable label.

29. The method of claim 28, wherein the detectable label is selected from the group consisting of ^{99m}Tc, ^{111}In, ^{123}I, ^{11}C, ^{18}F, ^{68}Ga, ^{76}Br, ^{61}Cu, ^{64}Cu, Gd, Fe, Mn and a fluorophore.

30. The method of claim 28, wherein the detecting step is performed using SPECT, 2-D planar gamma scintigraphy, PET, MRI, infrared detection, or a combination thereof.

31. A compound comprising a peptide chain approximately 8 to 40 amino acids in length that binds to VEGFR-2 and contains a sequence of amino acids of formula (III)

(III) GWX"$_1$GX"$_2$GX"$_3$H (SEQ ID NO: 3)

wherein each amino acid is indicated by standard one-letter abbreviation, and wherein X"$_1$ is L, I or R; X"$_2$ is V, L or I; and X"$_3$ is E or V.

32. The compound of claim 31, wherein the sequence of amino acids is selected from the group consisting of:

GWLGVGVH (SEQ ID NO: 144);

GWLGAGEHN (SEQ ID NO: 145);

GWLGVGEH (SEQ ID NO: 146);

GWLGLGEH (SEQ ID NO: 147);

GWIGLGVH (SEQ ID NO: 148); and

GWRGIGEH (SEQ ID NO: 149).

33. The compound of claim 32, wherein the sequence of amino acids is:
NASRISSGWLGVGVHNLSA (SEQ ID NO: 150);
SRRRHSTGWLGAGEHNLYS (SEQ ID NO: 151);
VIGRTWSGWLGVGVHNLSN (SEQ ID NO: 152);
QCGRVSSGWLGVGVHNLPF (SEQ ID NO: 153);
TNQRRSSGWLGVGVHTLSP (SEQ ID NO: 154);
GHKRASSGWLGVGVHKLSH (SEQ ID NO: 155);
HRRRMSSGWLGVGEHKLP (SEQ ID NO: 156);
SSGWLGVGVHYLSD (SEQ ID NO: 157);
QRRRSSSGWLGLGEHRL (SEQ ID NO: 158);
PQRRSSSGWIGLGVHDLFN (SEQ ID NO: 159);
SSRRASSGWRGIGEHNLYN (SEQ ID NO: 160); and
RCSSGWLGVGVHNLS (SEQ ID NO: 161).

34. The compound of claim 31, in the form of a dimer.

35. The compound of claim 31, wherein the N-terminus of the peptide is coupled to a polyethylene glycol molecule.

36. The compound of claim 31, wherein the N-terminus of the peptide is acetylated.

37. The compound of claim 31, wherein the C-terminus of the peptide is amidated.

38. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 31 in combination with a pharmaceutically acceptable carrier.

39. A method for treating a patient who would benefit from administration of a VEGFR-2 antagonist, comprising administering to the patient a therapeutically effective amount of a compound comprising a peptide chain approximately 8 to 40 amino acids that

binds to VEGFR-2 and contains a sequence of amino acids having the structural formula (III)

(III) $GWX"_1GX"_2GX"_3H$ (SEQ ID NO: 3)

wherein each amino acid is indicated by standard one-letter abbreviation, and wherein $X"_1$ is L, I or R; $X"_2$ is V, L or I; and $X"_3$ is E or V.

40. The method of claim 39, wherein the patient suffers from a disease selected from the group consisting of psoriasis, rheumatoid arthritis, retinopathy and cancer.

41. A method for imaging and assessing neovascularization during angiogenesis comprising administering a compound of claim 31 to a patient wherein the compound is coupled to a detectable label to form a labeled compound, allowing the labeled compound to bind to VEGFR-2, and detecting the detectable label.

42. The method of claim 41, wherein the detectable label is selected from the group consisting of ^{99m}Tc, ^{111}In, ^{123}I, ^{11}C, ^{18}F, ^{68}Ga, ^{76}Br, ^{61}Cu, ^{64}Cu, Gd, Fe, Mn and a fluorophore.

43. The method of claim 41, wherein the detecting step is performed using SPECT, 2-D planar gamma scintigraphy, PET, MRI, infrared detection, or a combination thereof.

SEQUENCE LISTING

<110> Affymax Research Institute
Schatz, Peter
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Mozsgai, Cecilia
Balu, Palani

<120> COMPOUNDS HAVING AFFINITY FOR THE VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR-2 (VEGFR-2) AND ASSOCIATED USES

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<223> Xaa is Val, Glu, Phe, Leu or Met

<220>
<221> UNSURE
<222> (11)..(11)
<223> Xaa is Glu, Asp or Val

<220>
<221> UNSURE
<222> (13)..(13)
<223> Xaa is Trp, Tyr or Phe

<220>
<221> UNSURE
<222> (14)..(14)

<223> Xaa is Ser, Ala, Glu, Gly, Thr, Trp, Val, Asn, Lys or Phe

<220>
<221> UNSURE
<222> (15)..(15)
<223> Xaa is Leu, His, Arg, Pro, Gln, Val, Met, Ser or Ile

<400> 1

Xaa Cys Xaa Xaa Xaa Xaa Xaa Gly Xaa Xaa Xaa Cys Xaa Xaa Xaa
1 5 10 15

<210> 2
<211> 8
<212> PRT
<213> Unknown

<220>
<223> unsure

<220>
<221> Unsure
<222> (2)..(2)
<223> Xaa is Trp or Gly

<220>
<221> Unsure
<222> (4)..(4)
<223> Xaa is Pro or Ala

<220>
<221> Unsure
<222> (5)..(5)
<223> Xaa is Glu or Asp

<220>
<221> Unsure
<222> (6)..(6)
<223> Xaa is Gly or Arg

<400> 2

Cys Xaa Gly Xaa Xaa Xaa Cys Trp
1 5

<210> 3
<211> 8
<212> PRT
<213> Unknown

<220>
<223> unsure

<220>
<221> Unsure
<222> (3)..(3)
<223> Xaa is Leu, Ile or Arg

<220>
<221> Unsure
<222> (5)..(5)
<223> Xaa is Val, Leu or Ile

<220>
<221> Unsure
<222> (7)..(7)
<223> Xaa is Glu or Val

<400> 3

Gly Trp Xaa Gly Xaa Gly Xaa His
1 5

<210> 4
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 4

Ser Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Trp Ser Leu
1 5 10 15

<210> 5
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 5

Ser Cys Trp Leu Gly Glu Tyr Gly Gly Glu Glu Cys Trp Ser His
1 5 10 15

<210> 6
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 6

Thr Cys Trp Ser Gly Glu Tyr Gly Gly Val Glu Cys Trp Ala Arg
1 5 10 15

<210> 7
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 7

Ser Cys Trp Pro Gly Asp Phe Gly Gly Val Glu Cys Trp Ser Leu
1 5 10 15

<210> 8
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 8

Tyr Cys Trp Pro Gly Glu Tyr Gly Gly Val Asp Cys Trp Ser Pro
1 5 10 15

<210> 9
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 9

Ser Cys Trp Ala Gly Glu Tyr Gly Gly Val Glu Cys Trp Ser Gln
1 5 10 15

<210> 10
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 10

Ala Cys Trp Thr Gly Glu Tyr Gly Gly Glu Glu Cys Trp Glu Leu
1 5 10 15

<210> 11
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 11

Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Trp Ala Val

1 5 10 15

<210> 12
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 12

Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Trp Gly Arg
1 5 10 15

<210> 13
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 13

Ser Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Trp Thr Val
1 5 10 15

<210> 14
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 14

Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Trp Ser Leu
1 5 10 15

<210> 15
<211> 15
<212> PRT
<213> Unknown

<220>
<223> Unsure

<400> 15

Ser Cys Trp Glu Gly Asp Asn Gly Gly Val Glu Cys Trp Trp Leu
1 5 10 15

<210> 16
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 16

Ala Cys Trp Pro Ser Glu Tyr Gly Gly Val Glu Cys Trp Ser Leu
1 5 10 15

<210> 17
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 17

Ser Cys Trp Pro Gly Glu Phe Gly Gly Val Glu Cys Trp Ser Val
1 5 10 15

<210> 18
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 18

Gln Cys Trp Pro Gly Asp Tyr Gly Gly Val Asp Cys Trp Ser Val
1 5 10 15

<210> 19
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 19

Thr Cys Trp Pro Gly Glu Tyr Gly Gly Glu Glu Cys Trp Ser Leu
1 5 10 15

<210> 20
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 20

Ser Cys Trp Pro Gly Glu Phe Gly Gly Phe Asp Cys Trp Ser Met
1 5 10 15

<210> 21
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 21

Val Cys Arg Pro Gly Glu Tyr Gly Gly Glu Glu Cys Trp Ser Leu
1 5 10 15

<210> 22
<211> 15
<212> PRT
<213> Unknown

<220>

<223> unsure

<400> 22

Ser Cys Trp Pro Ala Glu Tyr Gly Gly Val Glu Cys Trp Ser Met
1 5 10 15

<210> 23
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 23

Ser Cys Trp Pro Gly Glu Tyr Gly Gly Glu Glu Cys Tyr Trp Leu
1 5 10 15

<210> 24
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 24

Glu Cys Tyr Thr Asn Ala Ala Gly Val Leu Glu Cys Trp Val Ser
1 5 10 15

<210> 25
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 25

Thr Cys Trp Pro Gly Glu Tyr Gly Gly Glu Glu Cys Trp Ser Ile
1 5 10 15

<210> 26
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 26

Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr Ser Val
1 5 10 15

<210> 27
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 27

Ser Cys Trp Pro Gly Glu Tyr Gly Gly Glu Glu Cys Trp Ser Leu
1 5 10 15

<210> 28
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 28

Ser Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr Asn Val
1 5 10 15

<210> 29
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 29

Ser Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Trp Lys Leu
1 5 10 15

<210> 30
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 30

Ser Cys Trp Pro Ser Glu Tyr Gly Gly Glu Asp Cys Phe Asn Leu
1 5 10 15

<210> 31
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 31

Thr Cys Trp Pro Gly Glu Tyr Gly Gly Glu Val Cys Trp Ala Leu
1 5 10 15

<210> 32
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 32

Ser Cys Trp Pro Gly Glu Tyr Gly Gly Val Asp Cys Trp Ser Val
1 5 10 15

<210> 33

<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 33

Ser Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Trp Thr Leu
1 5 10 15

<210> 34
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 34

Tyr Cys Trp Pro Ala Glu Tyr Gly Gly Val Glu Cys Phe Ser Pro
1 5 10 15

<210> 35
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 35

Ala Cys Gly Pro Gly Glu Tyr Gly Gly Glu Glu Cys Trp Phe Val
1 5 10 15

<210> 36
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 36

Ser Cys Trp Thr Gly Glu Tyr Gly Gly Val Glu Cys Trp Thr Leu
1 5 10 15

<210> 37
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 37

Ser Cys Trp Pro Gly Glu Tyr Gly Gly Glu Val Cys Trp Ser Leu
1 5 10 15

<210> 38
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 38

Val Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Trp Asn Val
1 5 10 15

<210> 39
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 39

Ser Cys Gln Pro Gly Glu Tyr Gly Gly Met Val Cys Trp Ser Leu
1 5 10 15

<210> 40
<211> 15

<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 40

Val Cys Trp Pro Gly Glu Tyr Gly Gly Glu Asp Cys Trp Ser Leu
1 5 10 15

<210> 41
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 41

Ser Cys Phe Pro Ser Glu Tyr Gly Gly Glu Asp Cys Trp Ser Leu
1 5 10 15

<210> 42
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 42

Ser Cys Trp Glu Gly Glu Tyr Gly Gly Val Glu Cys Trp Ser Ile
1 5 10 15

<210> 43
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<220>

<221> Unsure
<222> (3)..(3)
<223> Xaa is 1-naphthylalanine

<400> 43

Thr Cys Xaa Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr Ser Val
1 5 10 15

<210> 44
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<220>
<221> Unsure
<222> (3)..(3)
<223> Xaa is 2-naphthylalanine

<400> 44

Thr Cys Xaa Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr Ser Val
1 5 10 15

<210> 45
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 45

Thr Cys Phe Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr Ser Val
1 5 10 15

<210> 46
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 46

Ala Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr Ser Val
1 5 10 15

<210> 47
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 47

Thr Cys Ala Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr Ser Val
1 5 10 15

<210> 48
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 48

Thr Cys Trp Pro Gly Ala Tyr Gly Gly Val Glu Cys Tyr Ser Val
1 5 10 15

<210> 49
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 49

Thr Cys Trp Pro Gly Glu Ala Gly Gly Val Glu Cys Tyr Ser Val

1 5 10 15

<210> 50
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 50

Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Ala Cys Tyr Ser Val
1 5 10 15

<210> 51
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 51

Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Ala Ser Val
1 5 10 15

<210> 52
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 52

Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr Ala Val
1 5 10 15

<210> 53
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 53

Ser Arg Glu Val Ser Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys
1 5 10 15

Trp Ser Leu Lys Glu
20

<210> 54
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 54

Ala Arg Val Val Ser Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys
1 5 10 15

Trp Ser Leu Asn Ser
20

<210> 55
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 55

Pro Gly Val Val Ser Cys Trp Leu Gly Glu Tyr Gly Gly Glu Glu Cys
1 5 10 15

Trp Ser His Asn Tyr
20

<210> 56
<211> 21
<212> PRT

<213> Unknown

<220>
<223> unsure

<400> 56

Phe Pro Leu Val Ser Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys
1 5 10 15

Trp Ser Leu Lys Thr
20

<210> 57
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 57

Thr Gly Val Val Thr Cys Trp Ser Gly Glu Tyr Gly Gly Val Glu Cys
1 5 10 15

Trp Ala Arg Asn Thr
20

<210> 58
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 58

His Arg Val Asp Ser Cys Trp Pro Gly Asp Phe Gly Gly Val Glu Cys
1 5 10 15

Trp Ser Leu Ser Glu
20

<210> 59

<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 59

Val Arg Val Glu Tyr Cys Trp Pro Gly Glu Tyr Gly Gly Val Asp Cys
1 5 10 15

Trp Ser Pro Lys Pro
20

<210> 60
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 60

His Gln Val Val Ser Cys Trp Ala Gly Glu Tyr Gly Gly Val Glu Cys
1 5 10 15

Trp Ser Gln Asn Ala
20

<210> 61
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unknown

<400> 61

Asn Arg Val Glu Ala Cys Trp Thr Gly Glu Tyr Gly Gly Glu Glu Cys
1 5 10 15

Trp Glu Leu Asn Leu
20

<210> 62
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 62

Ala Gly Gln Val Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys
1 5 10 15

Trp Ala Val Lys Tyr
20

<210> 63
<211> 18
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 63

Val Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Trp Gly Arg
1 5 10 15

Lys Gly

<210> 64
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 64

Glu Arg Val Ile Ser Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys
1 5 10 15

Trp Thr Val Asn Leu
20

<210> 65
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 65

Ser Arg Val Val Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys
1 5 10 15

Trp Ser Leu Glu Leu
20

<210> 66
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 66

Asn Arg Val Glu Ser Cys Trp Glu Gly Asp Asn Gly Gly Val Glu Cys
1 5 10 15

Trp Trp Leu Lys Tyr
20

<210> 67
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 67

Ser Gly Asp Val Ala Cys Trp Pro Ser Glu Tyr Gly Gly Val Glu Cys

1 5 10 15

Trp Ser Leu His Tyr
20

<210> 68
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 68

His Trp Glu Gly Ser Cys Trp Pro Gly Glu Phe Gly Gly Val Glu Cys
1 5 10 15

Trp Ser Val Asn Tyr
20

<210> 69
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 69

Asp Arg Met Gln Gln Cys Trp Pro Gly Asp Tyr Gly Gly Val Asp Cys
1 5 10 15

Trp Ser Val Asp Leu
20

<210> 70
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 70

His Arg Val Val Thr Cys Trp Pro Gly Glu Tyr Gly Gly Glu Glu Cys
1 5 10 15

Trp Ser Leu Gly Glu
20

<210> 71
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 71

Leu Asp Val Val Ser Cys Trp Pro Gly Glu Phe Gly Gly Phe Asp Cys
1 5 10 15

Trp Ser Met Lys Tyr
20

<210> 72
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 72

Asn Arg Val Leu Val Cys Arg Pro Gly Glu Tyr Gly Gly Glu Glu Cys
1 5 10 15

Trp Ser Leu Asp Tyr
20

<210> 73
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 73

Gly Gly Val Val Ser Cys Trp Pro Ala Glu Tyr Gly Gly Val Glu Cys
1 5 10 15

Trp Ser Met Asp Tyr
20

<210> 74
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 74

Gly Arg Val Glu Ser Cys Trp Pro Gly Glu Tyr Gly Gly Glu Glu Cys
1 5 10 15

Tyr Trp Leu Asp Ser
20

<210> 75
<211> 17
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 75

Arg Glu Glu Cys Tyr Thr Asn Ala Ala Gly Val Leu Glu Cys Trp Val
1 5 10 15

Ser

<210> 76
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 76

Pro Arg Val Val Thr Cys Trp Pro Gly Glu Tyr Gly Gly Glu Glu Cys
1 5 10 15

Trp Ser Ile Lys Tyr
20

<210> 77
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 77

Glu Arg Val Thr Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys
1 5 10 15

Tyr Ser Val Lys Tyr
20

<210> 78
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 78

Glu Trp Val Val Ser Cys Trp Pro Gly Glu Tyr Gly Gly Glu Glu Cys
1 5 10 15

Trp Ser Leu Lys Tyr
20

<210> 79
<211> 21
<212> PRT

<213> Unknown

<220>
<223> unsure

<400> 79

Lys Arg Val Val Ser Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys
1 5 10 15

Tyr Asn Val Lys Tyr
20

<210> 80
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 80

Thr Gln Val Glu Ser Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys
1 5 10 15

Trp Lys Leu Arg Tyr
20

<210> 81
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 81

Asp Gly Val Val Ser Cys Trp Pro Ser Glu Tyr Gly Gly Glu Asp Cys
1 5 10 15

Phe Asn Leu His Tyr
20

<210> 82

<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 82

Arg Pro Ser Glu Thr Cys Trp Pro Gly Glu Tyr Gly Gly Glu Val Cys
1 5 10 15

Trp Ala Leu Lys Tyr
20

<210> 83
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 83

Ser Tyr Val Glu Ser Cys Trp Pro Gly Glu Tyr Gly Gly Val Asp Cys
1 5 10 15

Trp Ser Val Lys Tyr
20

<210> 84
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 84

Pro Arg Val Val Ser Cys Trp Pro Gly Glu Tyr Gly Gly Val Asp Cys
1 5 10 15

Trp Ser Val Lys Tyr
20

<210> 85
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 85

Lys Arg Ala Val Ser Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys
1 5 10 15

Trp Thr Leu Glu Tyr
20

<210> 86
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 86

Met Arg Val Glu Tyr Cys Trp Pro Ala Glu Tyr Gly Gly Val Glu Cys
1 5 10 15

Phe Ser Pro Arg Asp
20

<210> 87
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 87

Ser Arg Val Leu Ala Cys Gly Pro Gly Glu Tyr Gly Gly Glu Glu Cys
1 5 10 15

Trp Phe Val Gln Tyr
20

<210> 88
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 88

Glu Thr Val Glu Ser Cys Trp Thr Gly Glu Tyr Gly Gly Val Glu Cys
1 5 10 15

Trp Thr Leu Asn Tyr
20

<210> 89
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 89

Val Leu Glu Val Ser Cys Trp Pro Gly Glu Tyr Gly Gly Glu Val Cys
1 5 10 15

Trp Ser Leu Lys Met
20

<210> 90
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 90

Ser Arg Val Glu Val Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys

1 5 10 15

Trp Asn Val Glu Ser
20

<210> 91
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 91

Gly Pro Val Val Ser Cys Gln Pro Gly Glu Tyr Gly Gly Met Val Cys
1 5 10 15

Trp Ser Leu Asn Tyr
20

<210> 92
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 92

Glu Ser Asp Val Val Cys Trp Pro Gly Glu Tyr Gly Gly Glu Asp Cys
1 5 10 15

Trp Ser Leu Asn Tyr
20

<210> 93
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 93

Gly Arg Val Val Ser Cys Phe Pro Ser Glu Tyr Gly Gly Glu Asp Cys
1 5 10 15

Trp Ser Leu Asn Tyr
20

<210> 94
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 94

Tyr Gln Val Glu Ser Cys Trp Glu Gly Glu Tyr Gly Gly Val Glu Cys
1 5 10 15

Trp Ser Ile Lys Leu
20

<210> 95
<211> 20
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 95

Arg Val Thr Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr
1 5 10 15

Ser Val Lys Tyr
20

<210> 96
<211> 19
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 96

Val Thr Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr Ser
1 5 10 15

Val Lys Tyr

<210> 97
<211> 18
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 97

Thr Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr Ser Val
1 5 10 15

Lys Tyr

<210> 98
<211> 17
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 98

Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr Ser Val Lys
1 5 10 15

Tyr

<210> 99
<211> 19
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 99

Arg Val Thr Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr
1 5 10 15

Ser Val Lys

<210> 100
<211> 18
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 100

Arg Val Thr Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr
1 5 10 15

Ser Val

<210> 101
<211> 22
<212> PRT
<213> Unknown

<220>
<223> unsure

<220>
<221> Unsure
<222> (20)..(20)
<223> Xaa is allyloxycarbonyl

<400> 101

Glu Arg Val Thr Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys
1 5 10 15

Tyr Ser Val Lys Xaa Tyr
20

<210> 102
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<220>
<221> Unsure
<222> (20)..(20)
<223> Xaa is allyloxycarbonyl

<400> 102

Arg Val Thr Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr
1 5 10 15

Ser Val Lys Xaa Tyr
20

<210> 103
<211> 21
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 103

Glu Arg Val Thr Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys
1 5 10 15

Tyr Ser Val Arg Tyr
20

<210> 104
<211> 20
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 104

Arg Val Thr Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr
1 5 10 15

Ser Val Arg Tyr
20

<210> 105
<211> 21
<212> PRT
<213> Unknown

<220>
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<400> 105

Glu Arg Val Thr Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys
1 5 10 15

Tyr Ser Val Ala Tyr
20

<210> 106
<211> 20
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 106

Arg Val Thr Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr
1 5 10 15

Ser Val Ala Tyr
20

<210> 107
<211> 20
<212> PRT

<213> Unknown

<220>
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<220>
<221> Unsure
<222> (6)..(6)
<223> Xaa is 1-naphthylalanine

<400> 107

Arg Val Thr Thr Cys Xaa Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr
1 5 10 15

Ser Val Lys Tyr
20

<210> 108
<211> 20
<212> PRT
<213> Unknown

<220>
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<220>
<221> Unsure
<222> (6)..(6)
<223> Xaa is 2-naphthylalanine

<400> 108

Arg Val Thr Thr Cys Xaa Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr
1 5 10 15

Ser Val Lys Tyr
20

<210> 109
<211> 20
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 109

Arg Val Thr Thr Cys Phe Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr
1 5 10 15

Ser Val Ala Tyr
20

<210> 110
<211> 20
<212> PRT
<213> Unknown

<220>
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<400> 110

His Val Thr Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr
1 5 10 15

Ser Val Arg Tyr
20

<210> 111
<211> 20
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 111

Gly Val Thr Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr
1 5 10 15

Ser Val Arg Tyr
20

<210> 112
<211> 20
<212> PRT

<213> Unknown

<220>
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<220>
<221> Unsure
<222> (1)..(1)
<223> Xaa is pyroglutamic acid

<400> 112

Xaa Val Thr Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr
1 5 10 15

Ser Val Arg Tyr
20

<210> 113
<211> 20
<212> PRT
<213> Unknown

<220>
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<220>
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<222> (6)..(6)
<223> Xaa is 1-naphthylalanine

<400> 113

Arg Val Thr Thr Cys Xaa Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr
1 5 10 15

Ser Val Ala Tyr
20

<210> 114
<211> 21
<212> PRT
<213> Unknown

<220>
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<220>
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<222> (7)..(7)
<223> Xaa is 1-naphthylalanine

<400> 114

Glu Arg Val Thr Thr Cys Xaa Pro Gly Glu Tyr Gly Gly Val Glu Cys
1 5 10 15

Tyr Ser Val Ala Tyr
20

<210> 115
<211> 20
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 115

Arg Val Ala Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr
1 5 10 15

Ser Val Ala Tyr
20

<210> 116
<211> 20
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 116

Arg Val Thr Ala Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr
1 5 10 15

Ser Val Ala Tyr
20

<210> 117
<211> 20
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 117

Arg Val Thr Thr Cys Ala Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr
1 5 10 15

Ser Val Ala Tyr
20

<210> 118
<211> 20
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 118

Arg Val Thr Thr Cys Trp Pro Gly Ala Tyr Gly Gly Val Glu Cys Tyr
1 5 10 15

Ser Val Ala Tyr
20

<210> 119
<211> 20
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 119

Arg Val Thr Thr Cys Trp Pro Gly Glu Ala Gly Gly Val Glu Cys Tyr

1 5 10 15

Ser Val Ala Tyr
20

<210> 120
<211> 20
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 120

Arg Val Thr Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Ala Cys Tyr
1 5 10 15

Ser Val Ala Tyr
20

<210> 121
<211> 20
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 121

Arg Val Thr Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Ala
1 5 10 15

Ser Val Ala Tyr
20

<210> 122
<211> 20
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 122

Arg Val Thr Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr
1 5 10 15

Ala Val Ala Tyr
20

<210> 123
<211> 20
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 123

Arg Val Thr Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr
1 5 10 15

Ser Val Arg Ala
20

<210> 124
<211> 8
<212> PRT
<213> Unknown

<220>
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<400> 124

Cys Trp Gly Pro Glu Gly Cys Trp
1 5

<210> 125
<211> 8
<212> PRT
<213> Unknown

<220>
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<400> 125

Cys Trp Gly Pro Asp Gly Cys Trp
1 5

<210> 126
<211> 8
<212> PRT
<213> Unknown

<220>
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<400> 126

Cys Gly Gly Pro Glu Gly Cys Trp
1 5

<210> 127
<211> 8
<212> PRT
<213> Unknown

<220>
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<400> 127

Cys Gly Gly Ala Glu Arg Cys Trp
1 5

<210> 128
<211> 16
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 128

Ser Asp Ser Val Asp Glu Cys Trp Gly Pro Glu Gly Cys Trp Leu Glu
1 5 10 15

<210> 129
<211> 16
<212> PRT
<213> Unknown

<220>
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<400> 129

Tyr Asn Thr Val Glu Asn Cys Trp Gly Pro Asp Gly Cys Trp Leu Asp
1 5 10 15

<210> 130
<211> 16
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 130

Met Ser Leu Val Asp Lys Cys Trp Gly Pro Glu Gly Cys Trp Leu Glu
1 5 10 15

<210> 131
<211> 19
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 131

Thr Ile Thr Val Gly Ser Cys Trp Gly Pro Glu Gly Cys Trp Leu Asp
1 5 10 15

Ser Arg Tyr

<210> 132
<211> 16
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 132

Ile Phe Leu Gly Glu Asn Cys Trp Gly Pro Asp Gly Cys Trp Leu Glu
1 5 10 15

<210> 133
<211> 16
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 133

Ile Arg Glu Gly Asp Met Cys Trp Gly Pro Glu Gly Cys Trp Val Asp
1 5 10 15

<210> 134
<211> 16
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 134

Leu Thr Leu Val Asp Asn Cys Trp Gly Pro Asp Gly Cys Trp Leu Glu
1 5 10 15

<210> 135
<211> 19
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 135

Glu Ser Arg Val Asp Asp Cys Trp Gly Pro Asp Gly Cys Trp Leu Asp
1 5 10 15

Pro Ile Thr

<210> 136
<211> 19
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 136

Val Glu Tyr Val Ala Asn Cys Gly Gly Ala Glu Arg Cys Trp Leu Gly
1 5 10 15

Thr Asn Met

<210> 137
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 137

Gln Asp Cys Trp Gly Pro Glu Gly Cys Trp Leu Gln Glu Gln Gly
1 5 10 15

<210> 138
<211> 16
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 138

Val Leu Asp Ala Asp Asn Cys Trp Gly Pro Glu Gly Cys Trp Leu Glu
1 5 10 15

<210> 139
<211> 16
<212> PRT

<213> Unknown

<220>
<223> unsure

<400> 139

Met Ser Glu Val Glu Asp Cys Trp Gly Pro Glu Gly Cys Trp Leu Glu
1 5 10 15

<210> 140
<211> 11
<212> PRT
<213> Unknown

<220>
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<400> 140

Asn Cys Trp Gly Pro Glu Gly Cys Trp Leu Glu
1 5 10

<210> 141
<211> 16
<212> PRT
<213> Unknown

<220>
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<400> 141

Ser His Arg Val Asp Asp Cys Trp Gly Pro Asp Gly Cys Trp Leu Glu
1 5 10 15

<210> 142
<211> 16
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 142

Ile Ile Glu Val Gly Asn Cys Trp Gly Pro Glu Gly Cys Trp Leu Glu
1 5 10 15

<210> 143
<211> 13
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 143

Val Asp Asn Cys Trp Gly Pro Glu Gly Cys Trp Leu Glu
1 5 10

<210> 144
<211> 8
<212> PRT
<213> Unknown

<220>
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<400> 144

Gly Trp Leu Gly Val Gly Val His
1 5

<210> 145
<211> 9
<212> PRT
<213> Unknown

<220>
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<400> 145

Gly Trp Leu Gly Ala Gly Glu His Asn
1 5

<210> 146
<211> 8
<212> PRT
<213> Unknown

<220>
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<400> 146

Gly Trp Leu Gly Val Gly Glu His
1 5

<210> 147
<211> 8
<212> PRT
<213> Unknown

<220>
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<400> 147

Gly Trp Leu Gly Leu Gly Glu His
1 5

<210> 148
<211> 8
<212> PRT
<213> Unknown

<220>
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<400> 148

Gly Trp Ile Gly Leu Gly Val His
1 5

<210> 149
<211> 8
<212> PRT
<213> Unknown

<220>
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<400> 149

Gly Trp Arg Gly Ile Gly Glu His

1 5

<210> 150
<211> 19
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 150

Asn Ala Ser Arg Ile Ser Ser Gly Trp Leu Gly Val Gly Val His Asn
1 5 10 15

Leu Ser Ala

<210> 151
<211> 19
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 151

Ser Arg Arg Arg His Ser Thr Gly Trp Leu Gly Ala Gly Glu His Asn
1 5 10 15

Leu Tyr Ser

<210> 152
<211> 19
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 152

Val Ile Gly Arg Thr Trp Ser Gly Trp Leu Gly Val Gly Val His Asn
1 5 10 15

Leu Ser Asn

<210> 153
<211> 19
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 153

Gln Cys Gly Arg Val Ser Ser Gly Trp Leu Gly Val Gly Val His Asn
1 5 10 15

Leu Pro Phe

<210> 154
<211> 19
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 154

Thr Asn Gln Arg Arg Ser Ser Gly Trp Leu Gly Val Gly Val His Thr
1 5 10 15

Leu Ser Pro

<210> 155
<211> 19
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 155

Gly His Lys Arg Ala Ser Ser Gly Trp Leu Gly Val Gly Val His Lys
1 5 10 15

Leu Ser His

<210> 156
<211> 18
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 156

His Arg Arg Arg Met Ser Ser Gly Trp Leu Gly Val Gly Glu His Lys
1 5 10 15

Leu Pro

<210> 157
<211> 14
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 157

Ser Ser Gly Trp Leu Gly Val Gly Val His Tyr Leu Ser Asp
1 5 10

<210> 158
<211> 17
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 158

Gln Arg Arg Arg Ser Ser Ser Gly Trp Leu Gly Leu Gly Glu His Arg

1 5 10 15

Leu

<210> 159
<211> 19
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 159

Pro Gln Arg Arg Ser Ser Ser Gly Trp Ile Gly Leu Gly Val His Asp
1 5 10 15

Leu Phe Asn

<210> 160
<211> 19
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 160

Ser Ser Arg Arg Ala Ser Ser Gly Trp Arg Gly Ile Gly Glu His Asn
1 5 10 15

Leu Tyr Asn

<210> 161
<211> 15
<212> PRT
<213> Unknown

<220>
<223> unsure

<400> 161

Arg Cys Ser Ser Gly Trp Leu Gly Val Gly Val His Asn Leu Ser
1 5 10 15

<210> 162
<211> 16
<212> PRT
<213> Unknown

<220>
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<400> 162

Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr Ser Val Lys Tyr
1 5 10 15

<210> 163
<211> 17
<212> PRT
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<220>
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<400> 163

Arg Val Thr Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr
1 5 10 15

Ser

<210> 164
<211> 16
<212> PRT
<213> Unknown

<220>
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<400> 164

Arg Val Thr Thr Cys Trp Pro Gly Glu Tyr Gly Gly Val Glu Cys Tyr
1 5 10 15